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PSEUDOMONAS BACTEREMIA: REVIEW OF NINETY-ONE CASES *

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INTRODUCTION

FOR several reasons, the role of bacteria of the *Pseudomonas* group in human disease has received increasing attention in recent years.[1-5] Antimicrobial drugs have reduced morbidity and mortality from many infections and have virtually eliminated several common pathogenic microorganisms as major threats to life. It is not surprising that therapeutic efforts now tend to focus upon those microbial species that remain poorly controlled by chemotherapy. With the possible exception of the hemolytic staphylococcus, the coliform and related gram-negative bacteria have been the most troublesome because of their irregular susceptibility to the drugs now available.[6,7] Among these bacilli, *Pseudomonas aeruginosa* is so notoriously resistant that it occupies an almost unique position. There is considerable evidence that serious gram-negative bacillary infections are occurring with greater frequency;[8,9] the incidence of pseudomonas bacteremia is rising.[8] This is in no small part attributable to ecologic changes wrought by antimicrobial drugs. It is now well recognized that the normal microflora of the human body maintains an important balance that in some way deters invasion by pathogens. This balance can be altered by antibiotic therapy,

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particularly by so-called broad spectrum coverage, which eliminates susceptible commensals and leads to unbridled multiplication of resistant "saprophytic" species. In this situation, "superinfection" by drug-resistant bacteria becomes likely. Prominent among the survivors are the *Pseudomonas* bacilli. Finally, as has been pointed out in connection with nosocomial staphylococcal infections, improved management has led to prolonged survival in many chronic diseases, and there has accumulated a large population of elderly, debilitated, and chronically ill patients whose resistance to bacterial infection is impaired. The susceptibility of these individuals can often be attributed to their primary disorder, but the use of radical surgery, ionizing radiation, and drugs which alter the leukocytic, inflammatory, or immune response are also factors of growing importance.

The many case reports and reviews that have been published on pseudomonas infection in man since its recognition as a pathogen by Charrin in 1890[10] indicate clearly that disease produced by these organisms is not a rarity. However, in view of the several factors already mentioned that have given added significance to pseudomonas infections in clinical medicine, a re-examination of their nature seems justified. It is the purpose of this report to review the problem of *Ps. aeruginosa* infection in man on the basis of an analysis of 91 cases of pseudomonas bacteremia observed at the Johns Hopkins Hospital. Bacteremia was chosen as the criterion for inclusion of cases for study because of the difficulty in evaluating the finding of these bacilli in cultures of localized inflammations of the skin, wounds, ear, eye, and elsewhere. We do not mean to imply that a positive blood culture is synonymous with generalized infection; indeed, among the patients included, there were several examples of transient or terminal bacteremia. However, one of the aims of this review has been to define the significance of culturing *Pseudomonas* from the blood in terms of the pathogenesis of infection, host factors in resistance, and relationship to antimicrobial drugs.

Clinical Material

The records of patients with pseudomonas bacteremia seen at the Johns Hopkins Hospital between July 1, 1940, and July 1, 1959, were examined. There were 91 episodes of bacteremia in 88 patients, with 73 deaths. Postmortem examinations were performed in 55 cases.

Records were scrutinized particularly for information about the portal of entry of the organism; concomitant infection or other diseases; prior therapy with antibiotics, antimetabolites, or adrenal corticosteroids; and other factors which conceivably could alter bacterial resistance.

Other data abstracted were the incidence of fever, rigors, peripheral vascular collapse, and skin lesions (especially ecthyma gangrenosum). The hemogram and all bacteriologic findings were noted, and the effectiveness of specific antimicrobial therapy was evaluated. Finally, an attempt was made to categorize the cases into those in which pseudomonas bacteremia was a

significant factor in the patient's morbidity or demise, and those in which it occurred as an incidental or agonal phenomenon.

Results

Ps. aeruginosa was isolated from the blood in all 91 cases; in 68 one or more ante-mortem cultures were positive; in the remaining 23 (20 small children and three adults) blood cultures taken immediately after death yielded *Pseudomonas*. In 16 of these 23 the blood had not been cultured prior to death. Histologic evidence of disseminated pseudomonas infection was present in 17 of those with positive post-mortem cultures; therefore, only six patients were included solely on the basis of *Pseudomonas* in heart-blood cultures at autopsy.

The patients fell into four distinct groups: 18 were premature infants, 27 were children with severe congenital or acquired diseases, 28 had lymphoma or leukemia, and 18 were adults with assorted chronic debilitating illnesses. The clinical course varied considerably among these groups, but was characteristic for each.

Premature infants (table 1)

Eighteen premature infants, whose average birth weight was 1,300 gm., comprised the first group. All but two (cases 3 and 15) were admitted to the hospital at birth or within two days thereafter. Only six survived for more than two weeks (cases 3, 8, 9, 14, 15, 18), and four of these ultimately died. The 12 infants who died before the fourteenth day had certain clinical features in common and will be considered first.

Infants who died in less than 14 days

There were eight males and four females among these infants. In three, ante-mortem blood cultures were positive for *Pseudomonas;* nine had positive post-mortem cultures.

Clinical Manifestations: Six infants had no clearly demonstrable portal of entry for *Pseudomonas*, two had infected umbilical stumps, and in four, areas of dermatitis or cellulitis were the initial site of infection. The illness of these babies was characterized by intermittent periods of apnea and cyanosis and failure to take nourishment. Fever was conspicuously absent. Jaundice was noted in seven, but this may have been a physiologic phenomenon. Four babies had pustular skin eruptions and one was covered with ecchymoses; in only one (case 2) were the dermal lesions typical of ecthyma gangrenosum.

Laboratory Data: Anemia was unusual, and white blood cell counts were not performed routinely. In three infants (cases 2, 11, 17) *Pseudomonas* was cultured from cerebrospinal fluid obtained immediately post-mortem; three had positive skin or stool cultures. In six children the blood stream

TABLE 1

Clinical Data in 18 Premature Infants*

Case	Year	Age	Sex	Prem. Birth/Wt.	Portal of Entry	Temp.	Chills	Shock	Anemia	WBC	*Pseudomonas* Cultures		Other Bacteremia
											Blood	Others	
1	1940	1 day	M	1,270 gm.	—	N	—	—	—	—	PM	0	Enterococcus (PM)
2	1940	1 day	F	870 gm.	Skin	N	—	—	—	—	PM	CSF (PM)	0
3	1946	16 days	M	1,450 gm.	G.I.	N	—	—	—	—	PM	Stool	0
4	1948	1 day	M	1,760 gm.	—	N	—	—	—	—	PM	0	0
5	1950	1 day	M	800 gm.	Umbil. cord	N	—	—	—	—	PM	Pustule, umbilicus	0
6	1951	1 day	M	1,660 gm.	—	N	—	—	—	—	AM	0	0
7	1951	1 day	F	1,360 gm.	Skin	N	—	—	—	—	AM	Stool, skin	0
8	1951	1 day	F	1,740 gm.	Skin	102[2]	—	—	—	23,000	AM ×2	Stool, abscess	0
9	1951	1 day	F	840 gm.	G.I.	101[2]	—	—	—	—	AM ×2	Stool	*A. aerogenes* (C)
10	1952	1 day	M	1,575 gm.	Skin	103[2]	—	—	—	—	PM	0	0
11	1953	1 day	F	1,240 gm.	—	N	—	—	—	—	PM	CSF (PM)	1) Strep. 2) *A. aerogenes* (C)
12	1953	1 day	M	920 gm.	Umbil. cord	N	—	—	—	—	PM	0	0
13	1954	1 day	M	1,360 gm.	—	N	—	—	—	10,000	PM	0	0
14	1956	2 days	M	1,500 gm.	G.I.	N	—	—	—	12,000	PM	Stool, urine	0
15	1956	18 days	M	1,800 gm.	G.I.	N	—	+	—	8,250	AM	Nose, stool	0
16	1957	1 day	F	1,675 gm.	Skin	N	—	—	—	—	PM	Pustule	0
17	1958	1 day	M	1,970 gm.	—	<96	—	—	0	—	AM	CSF (PM)	0
18	1958	1 day	F	1,240 gm.	Skin	<96	—	—	+	13,800	AM	Pustule	0

* Legends for Tables 1, 2, 3, 4: N = normal; — = unknown; 0 = negative; + = present; AM = ante-mortem; PM = post-mortem; (A) = antedecent to pseudomonas infection; (C) = concurrent with pseudomonas infection; (S) = subsequent to pseudomonas infection; P = penicillin; S = sulfa; St = streptomycin; C = chloramphenicol; T = tetracycline; Ery = erythromycin; PX = polymyxin; Neo = neomycin; Novo = novobiocin; Vanco = vancomycin; K = kanamycin; Myc = mycostatin; D = died; R = recovered; NP = nasopharynx; Fur = furadantin.

TABLE 1—*Continued*

Case	Year	Age	Sex	Antibiotics		Pathology		Significance	Result	Bacteriologic Cure	Comment
				Antecedent	Therapy	Diagnostic Lesions	Cultures				
1	1940	1 day	M	0	0	0	Blood	Terminal event	D	No	Icterus
2	1940	1 day	F	0	0	—	Blood	Contributory	D	No	?Ecthyma gangrenosum
3	1946	16 days	M	P	P	0	Lung	Contributory	D	No	—
4	1948	1 day	M	0	P, St	Lung	Blood	Contributory	D	No	—
5	1950	1 day	M	0	P, St	Lung	Blood	Contributory	D	No	Icterus
6	1951	1 day	M	P, St	P, St	0	Blood	Terminal event	D	No	Icterus
7	1951	1 day	F	P, St	P, St, C	0	Blood	Contributory	D	No	Icterus, pustular rash
8	1951	1 day	F	P, St T, C	P, St, T C, PX	—	—	Etiologic agent	R	Yes	Icterus, rash
9	1951	1 day	F	0	T, C	0	—	Not related to demise	D	Yes	Icterus
10	1952	1 day	M	P, St	P, St	0	—	Terminal event	D	No	Icterus, rash
11	1953	1 day	F	0	0	Lung, liver, pancreas	Blood, CSF	Contributory	D	No	—
12	1953	1 day	M	P, St	P, St	Umbilicus	Blood	Contributory	D	No	Icterus
13	1954	1 day	M	0	P, St, T	0	Blood	Terminal event	D	No	Icterus
14	1956	2 days	M	P, St	P, T, C	Lung, colon	Blood	Contributory	D	No	Icterus
15	1956	18 days	M	P, St, S, T Neo.	PX	Intestine	Blood, CSF	Etiologic agent	D	No	Icterus
16	1957	1 day	F	P, St	P, St	0	Blood	Contributory	D	No	Pyoderma: *Staph.* + *Ps. aeruginosa*
17	1958	1 day	M	P, St	C	Meninges	—	Etiologic agent	D	No	—
18	1958	1 day	F	0	C, Ery, Neo(Topical)	—	—	Etiologic agent	R	Yes	—

was the only site from which *Pseudomonas* was isolated. Post-mortem blood cultures were routine in this age group but ante-mortem cultures were obtained in only four of these 12 patients.

Treatment: Three of these patients received no therapy with antibiotics, in three no treatment was given during the initial phase of illness but chemotherapy was started before demise, while in the remainder antimicrobials were administered from birth. Since the outcome was uniformly fatal within a short period, it seems clear that the antibiotics did little to modify the course of the disease. The fact that six of these patients were receiving antibiotics before the development of sepsis suggests that these agents are of no prophylactic value.

Pathology: Post-mortem examinations were performed on 10 babies. Evidence that *Pseudomonas* was of pathogenetic importance was found in five cases (4, 5, 11, 13, 17) who had the vascular and necrotic lesions usually associated with infections with this organism or in whom the bacillus was present in sites other than heart blood. The remaining patients in this group had morphologic changes related primarily to prematurity.

Significance of Pseudomonas Infection: The presence of skin eruptions, infection of the umbilical stump, and pathognomonic lesions at autopsy were employed as criteria to determine whether *Pseudomonas* was of major importance in the demise of these children or whether they died as a result of prematurity. In eight of the 12 infants bacteremia was a contributory factor in the patient's death; in the remaining four, however, there was little evidence that invasion of the blood stream by *Pseudomonas* was more than an agonal manifestation.

PREMATURE INFANTS LIVING LONGER THAN 14 DAYS (TABLE 1, CASES 3, 8, 9, 14, 15, 18)

The other six premature infants presented a somewhat different clinical picture. Four died within one month after birth and two recovered.

Clinical and Pathologic Manifestations: In four of this group the gastrointestinal tract provided the portal of entry and in two the organism entered by way of the skin. *Pseudomonas* was isolated from sites other than the blood stream in every one of these children (stool: 5, skin: 1, urine: 1, and nasopharynx: 2). Jaundice was present in three. Diarrhea was a prominent clinical manifestation partially responsible for the death of two babies (cases 3 and 14). At autopsy, one had lesions in the colon and lung typical of pseudomonas infection while in the other the mucosa of the bowel was normal despite the fulminating diarrhea.

Laboratory Data: Anemia developed in all six of these babies, and leukocytosis was present in three. Case 9 had bacteremia with *Aerobacter aerogenes* as well as *Ps. aeruginosa.*

Treatment: Bacteriologic cure was achieved in three patients. One baby with pseudomonas dermatitis and bacteremia responded to chlor-

TABLE 2

Clinical Data in Children with Congenital and Acquired Diseases*

Case	Year	Age	Sex	Associated Pathology	Portal of Entry	Temp.	Chills	Shock	Anemia	WBC	Cultures		Other Bacteremia
											Blood	Other	
19	1945	1 mo.	M	Megacolon	G.I., skin	N	0	0	0	11,200	PM	NP CSF (PM)	0
20	1945	1 mo.	F	Sickle cell anemia, congenital syphilis	Ear	102[8]	0	0	+	14,000	AM	Ear	0
21	1945	6 mo.	M	Otitis media	Ear, G.I.	104	0	+	+	33,000	AM	CSF (PM)	(A) *Staph., E. coli,* enterococcus
22	1945	1 mo.	M	Staph. osteomyelitis	G.I.	102[8]	0	+	+	29,000	AM ×2	0	(A) *Staph.*
23	1945	9 mo.	M	Diarrhea	G.I.	105[6]	0	0	+	3,100	AM	Throat CSF (PM)	0
24	1945	4 mo.	F	Diarrhea, otitis media	Ear	103[2]	0	0	0	10,000	PM	Ear, CSF (PM)	0
25	1947	3 days	F	Agenesis myenteric plexus	G.I.	N	0	0	0	12,200	PM	0	0
26	1949	3 wks.	M	Multiple anomalies, urethral stricture	G.U.	102[8]	0	0	+	29,600	AM ×4	Urine	0
27	1950	8 mo.	M	Multiple anomalies	G.I.	N	0	0	0	16,000	PM	0	0
28	1950	5 yrs.	M	Hypospadias	G.U.	105	+	0	0	14,500	AM	Urine, kidney	0
29	1952	3 mo.	M	Diarrhea	G.I.	104	0	0	0	9,600	AM	Urine	(A) *E. coli*
30	1954	3 mo.	F	Mucoviscidosis	G.I., resp.	101[2]	0	0	0	25,000	PM	Nose, throat, stool	0
31	1955	3 yrs.	M	Mucoviscidosis	Lung	105[6]	0	0	0	13,000	PM	NP, throat	0
32	1956	4 days	M	Mucoviscidosis	G.I.	N	0	0	0	—	PM	Stool, trachea	0
33	1956	3 mo.	M	Diarrhea	G.I.	100[8]	0	0	+	22,000	AM	0	(C) *Proteus*
34	1956	5 yrs.	F	Congenital valve in portal vein	G.I.	103	0	0	+	—	PM	Pericardium, empyema (PM)	0
35	1957	7 yrs.	F	Ostium primum with SBE	Skin	105[6]	+	+	+	17,000	AM ×2	Skin	(A) *Staph.* (S) *Staph., Candida*
36	1958	1 mo.	M	Jaundice?, etiology?	—	N	0	0	+	8,400	AM	0	0
37	1958	16 days	M	Toxoplasmosis	Skin	101	0	0	0	200	AM	Scrotum, rectum, throat	0
38	1958	2 yrs.	M	Plumbism	G.U.	89	—	—	+	1,500	PM	—	0
39	1958	6 wks.	M	Diarrhea	G.I.	96	—	—	+	9,900	PM	—	0
40	1958	5 days	M	Intestinal obstruction, diarrhea	G.I.	96	—	—	0	6,600	AM ×2	—	0
41	1958	11 mo.	F	Rhabdomyosarcoma tongue; metastases to ovary, lymph nodes, pancreas, bones	G.I.	104	0	0	0	1,000	AM	Pharynx	0
42	1958	4½ yrs.	M	Nephrosis	G.U.	100	0	0	+	50,000	PM	CSF (PM) Ascitic fluid (PM), Urine (AM)	0
43	1958	13 yrs.	M	Nephrosis	Skin	102	0	0	+	18,500	AM	—	0
44	1958	11 yrs.	F	Mucoviscidosis	Resp.	103	0	0	+	24,000	PM	Sputum (AM)	0
45	1959	3 mo.	F	Cervical meningo-myelocele and post-operative hydro-cephalus	Skin	102	0	0	+	37,000	AM ×12	CSF ×3 wound ×4, throat	0

* Key to legends given above.

TABLE 2—*Continued*

Case	Year	Age	Sex	Antibiotics		Pathology		Significance	Result	Bacteriologic Cure	Comment
				Antecedent	Therapy	Diagnostic Lesions	Cultures				
19	1945	1 mo.	M	P S	P S	0	Blood, CSF	Contributory	D	No	Antecedent surgery
20	1945	1 mo.	F	P	P S	Thyroid, pericardium	—	Etiologic agent	D	No	Otitis media
21	1945	6 mo.	M	P S	P S	—	CSF	Contributory	D	No	Purpura
22	1945	1 mo.	M	P S	P S	0	—	Etiologic agent	D	No	Icterus, diarrhea
23	1945	9 mo.	M	0	P	Intestine, pharynx	Heart blood, CSF	Etiologic agent	D	No	Otitis media
24	1945	4 mo.	F	0	P	Intestine, adrenals, kidney, middle ear	Heart blood, CSF	Etiologic agent	D	No	—
25	1947	3 days	F	0	P S	Appendix, intestine	—	Contributory	D	No	Antecedent surgery, icterus
26	1949	3 wks.	M	0	P, St, S C, Px	Kidney	—	Contributory	D	Yes	Antecedent surgery
27	1950	8 mo.	M	P	P, St, C	0	Heart blood	Terminal event	D	No	Antecedent surgery
28	1950	5 yrs.	M	P	P, St, C	—	—	Etiologic agent	R	Yes	Antecedent cystoscopy, recovery after nephrectomy
29	1952	3 mo.	M	P, St	P, St, T	—	—	Contributory	D	No	—
30	1954	3 mo.	F	0	St, T, C Px	—	Lung, abscess, blood	Contributory	D	No	—
31	1955	3 yrs.	M	T Ery	P, T, C, Ery, Px	—	Lung	Contributory	D	No	Long term chemoprophylaxis
32	1956	4 days	M	0	0	—	Lung	Contributory	D	No	Antecedent surgery
33	1956	3 mo.	M	0	P, St, S, T	—	—	Etiologic agent	R	Yes	—
34	1956	5 yrs.	F	P C	P C	—	Heart blood, pericardium, empyema	Contributory	D	No	Antecedent leukopenia; surgery for portal hypertension with perforation of esophagogastric suture line
35	1957	7 yrs.	F	P, C, Ery, Novo	Vanco	0	—	Transient bacteremia	D	Yes	Infected cut-down; initial *Staph.* endocarditis; terminal *Candida* endocarditis
36	1958	1 mo.	M	0	0	—	—	Transient bacteremia	R	Yes	—
37	1958	16 days	M	C, P, Myc.	C, P, Myc.	Lung, testis	—	Contributory	D	No	Toxoplasmosis of brain, liver, heart
38	1958	2 yrs.	M	P	P	0	Heart blood	Term. bacteremia	D	No	Therapeutic hypothermia
39	1958	6 wks.	M	0	C	—	—	Prob. etiol. agt.	D	No	—
40	1958	5 days	M	0	C, St, S	—	—	Contributory	D	No	—
41	1958	11 mo.	F	P	P	Trachea, lung	—	Contributory	D	No	Antimetabolites and ionizing radiation
42	1958	4½ yrs.	M	P, St	P, St	—	—	Contributory	D	No	Antecedent steroids
43	1958	13 yrs.	M	T, C, P	T, C, P	Skin, rectum	—	Contributory	D	—	Subacute glomerulonephritis
44	1958	11 yrs.	F	P, C, Ery, Novo, St	Px	Trachea, lung	Heart blood, lung, trachea	Terminal bacteremia	D	No	Chronic *Pseudomonas* pulmonary infection
45	1959	3 mo.	F	0	C, St, S, P, K	—	—	Etiologic agent	D	No	—

amphenicol and topical application of neomycin; in another, who had a mixed bacteremia due to *A. aerogenes* and *Pseudomonas* the blood was sterilized by tetracycline and chloramphenicol; this child died unexpectedly following aspiration of gastric contents. A third infant who failed to improve following the administration of penicillin, streptomycin, chloramphenicol, and oxytetracycline recovered after polymyxin was added to the regimen.

CHILDREN WITH CONGENITAL ANOMALIES OR ACQUIRED DISEASES (TABLE 2)

Twenty-seven children ranging in age from three days to 13 years comprised this group. All were born after normal periods of gestation. There were 18 males and nine females. Thirteen had congenital defects; the remaining 14 had underlying acquired disease.

CHILDREN WITH CONGENITAL DEFECTS (TABLE 2, CASES 19, 20, 25–28, 30–32, 34, 35, 44, 45)

Of these, four had mucoviscidosis and two had multiple anomalies. Other congenital defects consisted of agenesis of the myenteric plexus, congenital lues and sickle cell anemia, hypospadias, portal hypertension due to a valve in the portal vein, congenital heart disease, and cervical meningomyelocele. All but one (case 28) died. In five children bacteremia was recognized prior to death; in the remaining eight *Ps. aeruginosa* was cultured after death.

Clinical Manifestations: The portal of entry for the organism could be established in every case; on several occasions more than one focus may have served as the initial site of infection. The organism was thought to enter via the gastrointestinal tract in seven patients; the ear, nose, or throat, lung, skin, urinary tract, and central nervous system were also implicated.

The clinical features of each patient's illness were dependent upon the underlying disease. For example, three of four children with mucoviscidosis succumbed to purulent pneumonitis and bronchiolitis; one baby with congenital stricture of the urethra developed azotemia and renal failure, and another with meningomyelocele died from meningitis and bacteremia. The symptoms of infants with congenital lesions involving the gastrointestinal tract were primarily diarrhea, abdominal distention, or obstipation. Fever was present in nine patients and jaundice in one. Because of the patients' ages, rigors and shock could not be accurately evaluated. There were no skin eruptions, although one patient developed cellulitis of the face while in the hospital. Eight underwent surgical procedures; these included resection or decompression of the stomach or bowel, manipulation of the urinary tract, and a shunting procedure to relieve hydrocephalus.

A 7-year-old girl (case 35) with staphylococcal endocarditis on an atrial septal defect developed an infection with *Pseudomonas* at a cut-down site, with ensuing bacteremia.

Laboratory Data: Anemia was present in six of the children, and in the 11 in whom white blood cell counts were performed leukocytosis was found. In all but two *Pseudomonas* was isolated from foci other than the blood stream.

Treatment: Five patients had received no antimicrobial therapy before developing infections. In two patients with mucoviscidosis who were on prophylactic antibiotics, pseudomonas pneumonia and bacteremia occurred.

All patients were treated with multiple antibiotics, including polymyxin B (cases 26, 30, 31, 44) and kanamycin (case 45). In one of these (case 26), a baby whose renal function was already compromised because of urethral strictures and megaloureter, marked oliguria and azotemia developed while he was receiving polymyxin B. Although the child died, there were no typical pseudomonas lesions at autopsy and culture of heart blood was sterile.

Only one patient in this group recovered (case 28). He developed bacteremia following cystoscopy for evaluation of hypospadias. Removal of a pyelonephrotic kidney resulted in cure; *Pseudomonas* was cultured from the surgical specimen. It should be noted that surgical extirpation of this focus of infection rather than chemotherapy was responsible for recovery.

The blood stream was cleared of bacteria in two patients who died subsequently. One has been described (case 26); the other had staphylococcal endocarditis followed by transient bacteremia with *Ps. aeruginosa* in the wake of massive antimicrobial therapy (case 35). Although *Pseudomonas* was eradicated from the blood stream, infection with *Candida tropicalis* supervened, and this fungus was cultured from the blood during life and from the heart valves at autopsy.

More frequent, however, was the persistence of *Pseudomonas* in the tissues, associated with repeated bouts of sepsis despite optimal chemotherapy. This was illustrated by a child with a meningomyelocele and an atrioventricular shunt (case 45) who had recurrent bouts of pseudomonas bacteremia complicated, terminally, by pseudomonas meningitis.

Pathology: Post-mortem examinations were performed in 11 of these cases. Lesions diagnostic of pseudomonas infection or positive cultures were present in the lungs of all four patients with mucoviscidosis. Typical microscopic lesions were seen in the thyroid and pericardium of the child with sickle cell anemia, and in the appendix and small bowel of the patient with agenesis of the myenteric plexus. Positive post-mortem cerebrospinal fluid cultures in two patients lent validity to the positive blood cultures obtained at autopsy. In one child (case 34) pseudomonas empyema and pericarditis developed following an esophagogastrectomy for bleeding esophageal varices.

Significance of Pseudomonas Infection: It is difficult to assess the contribution of pseudomonas bacillemia in patient with diseases which usually terminate fatally. Certainly death was prevented in the boy with

hypospadias by control of the infection. Similarly, pseudomonas endocarditis hastened the end in a girl with congenital heart disease. Of the 12 patients who died, only one can be said to have had pseudomonas sepsis as an agonal phenomenon. In the remainder, infection was instrumental in demise.

CHILDREN WITH ACQUIRED DISEASES PREDISPOSING TO INFECTION (TABLE 2, CASES 21–24, 29, 33, 36–43)

These patients ranged in age from five days to 13 years; 12 were males and two were females. All but two of these children died, and in five death was related to lethal associated disease such as toxoplasmosis (case 37), lead poisoning treated with hypothermia (case 38), rhabdomyosarcoma of the tongue treated with x-ray and antimetabolites (case 41), and nephrosis (cases 42 and 43). Two children recovered. One (case 36) was admitted for jaundice of unknown etiology; a routine blood-culture grew *Pseudomonas*. He recovered without specific therapy and must be considered to have had the transient bacteremia sometimes seen in patients with hepatic disease.[12] Ten patients had positive *Pseudomonas* blood cultures before death; in the four with positive post-mortem cultures there was collateral evidence of infection.

Clinical Manifestations: In the six patients described above (Table 2, cases 36–38, 41–43), the clinical picture was dominated by the underlying illness, but the remaining eight had symptoms referable to the gastrointestinal tract. In this group diarrhea was the predominant symptom. Two of these children also had otitis media with *Pseudomonas* and another had osteomyelitis from which *Staphylococcus aureus* was cultured. Fever was usually present, with temperatures as high as 105.6° F. Two babies with diarrhea had temperatures lower than 96° F. Peripheral vascular collapse was observed in two instances of bacteremia, and purpura once. Two patients were icteric.

Laboratory Data: Anemia was present in nine of these 14 children. There was great variability in the leukocyte counts, which were elevated to between 15,000 and 33,000/cu. mm. in five patients, and were normal in six. Leukopenia was noted three times but could be attributed to bacteremia per se only once, since one patient had toxoplasmosis and the other had received ionizing radiation and antimetabolic drugs. Thrombocytopenia was not a prominent finding and, clinically, only one patient had a tendency to hemorrhage.

Four children had mixed bacteremias with organisms in addition to *Pseudomonas*. In one (case 19) *Staph. aureus, Escherichia coli,* and enterococci were isolated from several blood cultures prior to pseudomonas bacteremia. A second baby with osteomyelitis and bacteremia due to *Staph. aureus* received penicillin and sulfadiazine and improved, but finally developed a superinfection with *Pseudomonas*.

One child had *Proteus* species cultured from the blood concomitantly with *Pseudomonas* and in another *Esch. coli* preceded bacteremia with *Pseudomonas.*

Cerebrospinal fluid obtained immediately after death in four patients yielded *Ps. aeruginosa* on culture. The ears or throat served as the portal of entry for meningitis in three cases; in a fourth child with nephrosis, ascitic fluid and urine as well as the cerebrospinal fluid contained *Pseudomonas* bacilli.

Despite the prevalence of diarrhea in eight of these babies, two of whom had lesions pathognomonic of pseudomonas enterocolitis at autopsy, the organism was not found in the fecal flora. This may, however, reflect failure to report this organism in stool specimens unless it predominates. Failure to find *Pseudomonas* in feces was not universal, since 11 patients in the entire study had one or more positive stool cultures; three of these had lesions in the bowel as well.

Treatment: Three patients were receiving antibiotic therapy for bacteremia with other organisms prior to pseudomonas infection (cases 21, 22, 29); all died. One patient with jaundice and transient bacteremia recovered spontaneously (case 36) and another, a 4-month-old infant with severe diarrhea and bacteremia due to *Proteus* and *Pseudomonas* (case 33), recovered following vigorous antimicrobial and fluid therapy.

Unfortunately, this case was exceptional. More representative were several infants who died because of persistent diarrhea despite vigorous therapy.

Pathology: Autopsies were performed on seven patients. Two did not have diagnostic lesions of infection with *Pseudomonas;* in five others, however, there were classical lesions in the bowel, pharynx, trachea, lung, and testes (cases 23, 24, 37, 41, 43). The histologic appearance of lesions in the bowel was similar to the acellular, necrotic lesions produced by *Pseudomonas* elsewhere in the body. Lesions in the bowel in these patients were identical with those described by Schaffer and Oppenheimer[13] in cases of infantile diarrhea due to *Pseudomonas.*

Significance of Infection: In contrast to premature infants and patients with leukemia, pseudomonas infection played a major role in determining the outcome of this group. In only two patients—the baby with jaundice of unknown etiology and the child with plumbism—was infection with this organism not of pathogenetic significance. In four patients with diarrhea, pseudomonas colitis and bacteremia were undoubtedly the mechanisms of death. Although eight patients were severely ill, most of them with lethal disease, the advent of death was probably accelerated by the development of psudomonas infection.

PATIENTS WITH LEUKEMIA (TABLE 3)

Twenty-five patients with leukemia had 28 episodes of pseudomonas bacteremia. In 21 cases the leukemic process was in the acute phase; other

TABLE 3

Clinical and Pathologic Data in Patients with Leukemia*

Case	Year	Age	Sex	Associated Pathology	Portal of Entry	Temp.	Chills	Shock	Anemia	WBC	Cultures		Other Bacteremia
											Blood	Other	
46	1943	4½ yrs.	M	Acute leukemia	—	105[3]	0	0	++	(A)1,320	AM X2	CSF (PM)	(A) *Staph.*
47	1947	4½ yrs.	F	Aplastic anemia	G.I.	105[3]	0	0	++++	(A)450	AM	Stool	0
48	1949	3 yrs.	M	Reticuloendotheliosis	G.I.	104	0	0	++++	(A)960	AM	Stool, nose, throat	0
49	1950	1 yr.	F	Acute leukemia	Skin	104	0	0	++++	(A)3,900	AM X3	Stool, hematoma	0
50	1950	7 yrs.	M	Aleukemic leukemia	—	105[4]	0	0	+++	(A)900	AM X3	0	(A) *Enterococcus*
51	1950	9¾ yrs.	F	Acute lymphatic leukemia	Resp.	105[4]	0	0	+++	3,500	AM X2	Stool, throat, vagina	0
52	1950	4 yrs.	M	Acute lymphatic leukemia	Skin	103[3]	0	0	++	(A)400	AM	0	(A) *E. coli*
53	1950	4 yrs.	M	Acute lymphatic leukemia	Skin	104	0	0	++	(A)950	AM X2	CSF (PM)	0
54	1953	4½ yrs.	F	Acute lymphatic leukemia	Ear	105[3]	0	0	o	18,200	AM X3	Ear, nose, throat	(A) *Staph.*
55	1954	48 yrs.	M	Acute myeloid leukemia	G.I.	103	0	0	+++	23,000	PM	0	0
56	1955	4 yrs.	F	Acute leukemia	Skin	105[4]	0	0	+++	(A)700	AM X2	Ankle, hand	(A) *Staph.*
57	1955	4 yrs.	F	Acute leukemia	Bone	104	0	+	+++	(A)650	AM	0	(C) Diphtheroids
58	1955	19 yrs.	F	Chronic myeloid leukemia	Resp.	105	0	0	+++	(A)900	AM X2	0	0
59	1955	46 yrs.	F	Acute leukemia	Resp.	104	0	0	+++	11,000	AM	Sputum	(A) *Staph.*
60	1956	10 yrs.	M	Acute leukemia	—	104[4]	0	0	+++	(A)2,800	AM X2	0	(A) *Staph.*
61	1956	4 yrs.	F	Acute leukemia	Ear	105[3]	0	0	++	(A)650	AM	Ear	(S) *Enterococcus*
62	1956	12 yrs.	M	Acute leukemia	G.I.	105[3]	0	0	+	(A)600	AM	0	(A) Diphtheroids
63	1956	2 yrs.	F	Acute leukemia	Resp.	106[4]	0	0	+	(A)1,200	AM X2	Nasopharynx,	(C) *E. coli*
64	1957	62 yrs.	M	Acute monocytic leukemia	Resp.	102[3]	0	+	+++	(A)825	AM	Sputum	(A) *Staph.*
65	1957	57 yrs.	M	Acute monocytic leukemia	Resp.	105[4]	+	o	+++	(A)385	AM X3	Sputum	(S) *Paracolon*
66	1957	52 yrs.	M	Acute lymphatic leukemia	Skin	104	o	+	+++	(A)900	AM	—	(A) *A. aerogenes*
67	1958	53 yrs.	M	Acute lymphatic leukemia	—	104	+	o	+++	(A)300,000	AM	—	0
68	1958	11 yrs.	M	Acute leukemia	—	104	o	+	+++	(A)700	AM	—	0
69	1958	4 yrs.	M	Acute leukemia	—	103	o	o	+++	(A)600	AM, PM	—	0
70	1959	50 yrs.	M	Monocytic leukemia	Skin	105	0	0	++	(A)1,800	AM X2	Throat, sputum, rectum	0
71	1959	55 yrs.	M	Chronic lymphatic leukemia	—	105	0	0	+	100,000	AM X2	—	(A) *Pneumococcus*
72	1959	70 yrs.	M	Subacute lymphatic leukemia	—	104	0	0	+	(A)2,000	AM X2	—	0
73	1959	17 yrs.	F	Acute aleukemic leukemia	G.U.	105	0	0	+	2,500	PM	Urine	0

* Key to legends given above.

TABLE 3—*Continued*

Case	Year	Age	Sex	Antibiotics		Pathology		Significance	Result	Bacteriologic Cure	Comment
				Antecedent	Therapy	Diagnostic Lesions	Cultures				
46	1943	4½ yrs.	M	P	P S	0	CSF (PM)	Contributory	D	No	—
47	1947	4½ yrs.	F	P, St, S	P, St, S	Ovary, intestines, lymph nodes	Heart blood	Etiologic agent	D	No	—
48	1949	3 yrs.	M	0	P, St, S	0	—	Contributory	D	Yes	—
49	1950	1 yr.	F	T	P, St, S, T, C	0	—	Transient bacteremia	D	Yes	Steroids (A)
50	1950	7 yrs.	M	P, S, T	C	Intestine	Heart blood	Contributory	D	No	Steroids (A)
51	1950	9½ yrs.	F	0	P, St, S, C	—	—	Contributory	D	No	—
52	1950	4 yrs.	M	P, St	P, St, S	—	—	Etiologic agent	R	Yes	—
53	1950	4 yrs.	M	P	T, St, C	—	Heart blood, CSF, kidney	Contributory	D	No	Antileukemic drugs (A)
54	1953	4½ yrs.	F	T	P, Px	Intestine	—	Contributory	D	No	Steroids and antileukemic drugs (A)
55	1954	48 yrs.	M	P S	P S	Intestine	—	Contributory	D	No	Steroids and antileukemic drugs (A)
56	1955	4 yrs.	F	T	St, C	—	—	Etiologic agent	R	Yes	Infected site of infusion, steroids and antileukemic (A) drugs
57	1955	4 yrs.	F	T, C, Ery	T, C, Ery	0	Wrist	Terminal event	D	No	Infected site of infusion, steroids and antileukemic (A) drugs
58	1955	19 yrs.	F	P, T, C	P, T, C	—	—	Contributory	D	No	Infected site of infusion, steroids and antileukemic (A) drugs
59	1955	46 yrs.	F	T	P, T, Ery, Px	—	Lung	Contributory	D	No	—
60	1956	10 yrs.	M	P	Ery, Novo	Colon, small intestine, tongue	Heart blood	Contributory	D	No	Steroids and antileukemic drugs (A)
61	1956	4 yrs.	F	P, St, Novo	St, Px	—	—	Transient bacteremia	D	Yes	Steroids and antileukemic drugs (A)
62	1956	12 yrs.	M	P C	P C	Colon	Heart blood	Contributory	D	No	Steroids and antileukemic drugs (A)
63	1956	2 yrs.	F	P, St, C Novo	P, S, C, Px	0	—	Etiologic agent	D	Yes	Died of paracolon septicemia 3 months later
64	1957	62 yrs.	M	P, St, C	P, St, C	—	—	Terminal superinfection	D	No	Diabetes mellitus, steroids and antileukemic drugs (A)
65	1957	57 yrs.	M	T	P, St, C, Ery	—	—	—	D	No	Steroids and antileukemic drugs (A)
66	1957	52 yrs.	M	S	C, St, T, P	—	—	Etiologic agent	R	Yes	Steroids and antileukemic drugs (A). Recovery coincident with remission
67	1958	53 yrs.	M	0	0	Lungs	—	Contributory	D	No	Steroids and antileukemic drugs (A)
68	1958	11 yrs.	M	T	T	Colon, meninges, brain abscess	Blood, colon, brain	Contributory	D	No	Steroids and antileukemic drugs (A)
69	1958	4 yrs.	M	P, St	P, St	—	—	Terminal	D	No	X-ray and nitrogen mustard (A)
70	1959	50 yrs.	M	P, C, K	St, C	—	—	—	R	Yes	Steroids, x-ray, and antileukemics (A). Massive antimicrobial therapy
71	1959	55 yrs.	M	P, C	C	—	Lung, blood	Contributory	D	No	Hypogammaglobulinemia (5%), post-pneumococcal superinfection
72	1959	70 yrs.	M	C, St	Neo, C, St	—	—	Contributory	D	No	Antileukemic drug (TEM), (A)
73	1959	17 yrs.	F	P, St, K, Myc.	Same	Lung	Heart blood	Contributory	D	No	Steroid therapy, associated moniliasis of esophagus, mouth and vagina

diagnoses were reticuloendotheliosis, aplastic anemia, chronic myelogenous leukemia, and chronic lymphatic leukemia. Fifteen in this group were children age one to 12, and nine were adults, eight of whom were older than 40. Among the children there were eight males and seven females, but in the adult group seven of 10 patients were male. As might be expected, 24 of the 25 died, the only survivor being a 55-year-old man with monocytic leukemia who is being maintained on adrenal hormones and antimetabolites. Nevertheless, sterilization of the blood stream was accomplished eight times.

Blood cultures were positive for *Pseudomonas* prior to death in all except two patients. In these cases, however, positive post-mortem blood cultures were corroborated by pathognomonic lesions. During 13 bouts of bacteremia, multiple cultures were positive. As a rule sepsis occurred during the last week of life, but in eight patients cultures became negative prior to death. Three patients had two bouts of bacteremia separated by intervals of from three to 12 months.

Clinical Manifestations: The organism gained access to the blood stream by a variety of routes. The skin or subcutaneous tissues served as the portal of entry in seven patients; the respiratory tract was the source of infection six times, the alimentary canal twice, one child had an indolent focus of osteomyelitis of the wrist, and one patient had persistent bacteriuria. Eight bouts of sepsis occurred in the absence of a demonstrable portal of entry. In several patients, particularly those with leukopenia, the cutaneous lesions were characteristically shallow, ragged ulcerations in the scrotal and perineal regions which drained serous exudate but which were free of pus. One infant (case 49) developed a pseudomonas infection at the site of a bone marrow biopsy.

In general, the outcome of the infection paralleled closely the patient's hematologic status, and bacteriologic cure was accompanied or preceded by remission of the leukemic process in three of four patients who made a transient recovery from pseudomonas sepsis. The exception was a 50-year-old man (case 70) with monocytic leukemia who survived the infection, probably as a result of vigorous treatment with 6 gm. of chloramphenicol and 2 gm. of streptomycin per day. He did not experience hematologic remission until three months after the bout of bacteremia. Conversely, sterilization of the blood stream did not modify the fatal outcome unless improvement in the leukemic process occurred simultaneously, and four patients with "bacteriologic cures" died despite eradication of the infection. The close relationship between the course of the leukemia and the superimposed infection is illustrated by a 4-year-old girl who developed pseudomonas osteomyelitis and bacteremia following infiltration of a transfusion into the tissues of the hand. Concomitant with hematologic remission, blood cultures became sterile although the osteomyelitic focus remained evident by x-ray. Four months later a flare-up of the leukemic process oc-

curred and at the same time there was a recrudescence of carpal osteomyelitis and pseudomonas sepsis.

Fever was uniformly present in this group and temperatures over 105° F. were recorded during 12 bouts of bacteremia. Shock, best explained by septicemia, was noted in only three patients, and true rigors were recorded in two others. Since pyrexia is almost invariable in uncontrolled acute leukemia, its significance is difficult to assess. On the other hand, in the absence of hemorrhage, the occurrence of shock was probably a manifestation of bacteremia, as were the shaking chills. The pathogenic importance of purpura and icterus noted in several patients was equally difficult to evaluate in the face of severe thrombocytopenia and hemolysis.

Laboratory Data: Anemia was present in 24 of 25 patients. The leukocyte picture was abnormal in every case. Twenty-three patients had an absolute leukopenia of from 350 to 3,500 WBC/cu. mm. and most of the cells consisted of immature forms. In 22 of these 23 cases leukopenia antedated the development of pseudomonas infection, and in only one patient was the fall in leukocyte count attributable to sepsis. The other five patients had white counts of 11,000, 18,200, 23,000, 100,000 and 300,000/cu. mm., and the majority of cells were abnormal. No patient developed *Pseudomonas* infection while in hematologic remission. Thrombocytopenia invariably accompanied leukopenia.

Bacteremia with other organisms was observed 15 times in 11 patients. These blood stream infections antedated pseudomonas bacillemia in 11 instances, on two occasions *Pseudomonas* was cultured simultaneously with diphtheroids and *Esch. coli,* and two patients had blood cultures positive for other bacteria subsequent to the pseudomonas infection (Table 4). In one patient (case 73) autopsy revealed significant concurrent candidiasis. One patient had diphtheroidemia followed by bacteremia with *Esch. coli* and *Ps. aeruginosa.*

Pseudomonas was cultured from sites other than blood in 14 patients. Cultures of the stool were positive four times, throat five times, sputum four times, ear, skin, and cerebospinal fluid twice each, and urine once.

Treatment: In only three instances did therapy with antibiotics fail to precede the onset of pseudomonas bacillemia. In addition, 17 were receiving 6-mercaptopurine, anti-folic agents, or nitrogen mustards at the time of infection, and 17 were being treated with adrenal corticosteroids. In 26 of 28, pseudomonas bacteremia occurred in patients receiving antibiotics adrenal hormones, or antileukemic therapy.

A variety of antimicrobials was used in an attempt to control pseudomonas bacteremia, usually without success. In 27 episodes of sepsis treated with antibiotics the blood stream was cleared of bacteria only eight times despite therapy with multiple drugs. Usually several agents were employed; a single drug was used in only three infections, while two drugs were employed eight times, three drugs nine times, and four or more agents in

seven instances. Inasmuch as it is difficult to designate any one drug as being responsible for successful treatment, credit was assigned to all agents when sterilization of the blood was achieved. In general, streptomycin, polymyxin B, and sulfonamides were the most effective agents. Chloramphenicol, tetracycline, and pencillin were occasionally of value. At best, however, bacteriologic cures were achieved in less than one-third of patients treated. This abysmal result is probably a consequence of the breakdown of host defenses associated with leukemia. Furthermore, *Pseudomonas* is inherently resistant to antibiotics and growth of most strains is not inhibited by antibiotics in vitro.[14] The role of antibiotics in controlling this infection was subordinate to the course of the underlying disease and despite eight "bacteriologic cures" only four patients survived the episode of sepsis and three of these died within a few months.

Pathology: Post-mortem examinations were performed in 17 patients, nine of whom had pathognomonic lesions. The necrotic acellular ulcers described previously were noted in the intestine in seven patients; in two cases the lungs were the only organs involved. Cultures of heart blood were positive eight times at autopsy, and in eight patients the cerebrospinal fluid also contained bacteria. One patient had a brain abscess. In three of four patients who had no morphologic or bacteriologic evidence of antecedent pseudomonas infections, the blood stream had been sterilized prior to death. For example, a girl who had recovered from pseudomonas bacteremia died of generalized infection with paracolon bacilli three months later (case 63).

Significance of Pseudomonas Infection: As has been indicated, all patients in this group had a fatal disease. Nevertheless, intercurrent pseudomonas infection was an important cause of morbidity and certainly hastened death in some cases. Only once did it seem to be an agonal phenomenon.

ADULTS WITH PSEUDOMONAS BACTEREMIA (TABLE 4)

Eighteen adults, 16 of them males with a diversity of acute and chronic illness, were in this group. The median age was 60, and all but three were older than 50. Eight of these patients had disease of the urinary tract, and there were seven instances of malignancy complicated by pseudomonas sepsis. Diabetes mellitus was present in two patients but both had other diseases which predisposed to secondary infection. Seventeen of 18 patients had positive blood cultures ante-mortem, and in six of them multiple cultures were positive.

Leukopenia antedated bacteremia in three patients. It was associated with rheumatoid arthritis in one, with gout and a drug reaction in another, and with treated Hodgkin's disease in a third. In one patient with eczema, who was being treated for pyoderma and staphylococcal septicemia, *Pseudomonas* was clearly a superinfection, and in another who developed a subphrenic abscess after subtotal gastrectomy the same train of events probably obtained. A 26-year-old female, reported in detail previously, developed

TABLE 4

Clinical Data in 18 Adults with *Pseudomonas* Sepsis*

Case	Year	Age	Sex	Associated Pathology	Portal of Entry	Temp.	Chills	Shock	Anemia	WBC	Cultures		Other Bacteremia
											Blood	Other	
74	1940	35 yrs.	M	Hydronephrosis	G.U.	104[6]	+	0	0	17,000	AM	0	0
75	1940	70 yrs.	M	Carcinoma bladder	G.U.	103[6]	0	0	0	29,000	AM	Urine	0
76	1941	69 yrs.	M	Carcinoma bladder	G.U.	103	0	0	0	12,400	AM×2	Urine	0
77	1944	61 yrs.	M	Diabetes mellitus	G.U.	105	0	0	+	20,000	AM	Urine	0
78	1946	62 yrs.	M	Biliary obstruction	Biliary tract	105[6]	+	0	+	24,000	AM×3	Gall-bladder	(A) *E. coli, Enterococcus*
79	1947	26 yrs.	F	Traumatic A-V fistula	G.U.	105	+	0	0	10,000	AM×6	Urine	0
80	1947	60 yrs.	M	Prostatic hypertrophy	G.U.	104	+	0	0	—	AM	Urine	0
81	1948	50 yrs.	M	Urethral stricture	G.U.	104[4]	+	0	0	16,000	AM×5	Urine, wound	0
82	1948	69 yrs.	M	Carcinoma prostate	G.U.	105	+	0	0	—	AM	Urine	0
83	1948	60 yrs.	M	Subtotal gastrectomy and subphrenic abscess	G.I.	102	+	+	0	33,000	AM	Urine, sputum, pleural fluid, subphrenic abscess	0
84	1949	78 yrs.	M	Carcinoma prostate, uremia	G.U.	104	+	+	0	20,000	AM	Urine	(C) *A. aerogenes Enterococcus*
85	1956	73 yrs.	M	Rheumatoid arthritis	Skin	104	+	0	0	(A)1,450	AM×2	Throat	0
86	1957	51 yrs.	M	Gout, dermatitis, pancytopenia 2°, Colcemid	Skin	104	0	+	+	(A)300	AM	Conjunctiva, scrotum	0
87	1957	15 yrs.	M	Eczema with pyoderma	Skin	105[2]	+	0	0	12,000	AM×2	0	(A) *Staphylococcus*
88	1957	58 yrs.	M	Hodgkin's disease	—	97	0	+	+	(A)1,600	AM	0	0
89	1957	55 yrs.	F	Pyelonephritis	G.U.	104[2]	+	0	+	33,800	AM	Urine	0
90	1959	70 yrs.	M	Carcinoma lung	—	102	0	0	+	8,400	AM	—	0
91	1959	56 yrs.	M	Carcinoma lung	Resp.	103[6]	0	+	+	2,700	PM	Sputum, empyema	0

* Key to legends given above.

TABLE 4—*Continued*

Case	Year	Age	Sex	Antibiotics		Pathology		Significance	Result	Bacteriologic Cure	Comment
				Antecedent	Therapy	Diagnostic Lesions	Cultures				
74	1940	35 yrs.	M	0	0	—	—	Transient bacteremia	R	Yes	Antecedent surgery
75	1940	70 yrs.	M	S	S	—	—	Transient bacteremia	R	Yes	Antecedent urologic surgery
76	1941	69 yrs.	M	0	S	—	—	Etiologic agent	R	Yes	Antecedent urologic surgery
77	1944	61 yrs.	M	P, S	P	—	—	Terminal event	D	No	Indwelling catheter
78	1946	62 yrs.	M	0	P, St	—	—	Etiologic agent	R	Yes	Recovered after cholecystostomy. Died 6 mo. later.
79	1947	26 yrs.	F	0	P, St, S	A-V fistula aortic valve	Lung, heart	Etiologic agent	D	No	Antecedent surgery and urologic study
80	1947	60 yrs.	M	P	P, St	—	—	Transient bacteremia	R	Yes	Antecedent urologic surgery
81	1948	50 yrs.	M	P	P, St, Px	—	—	Etiologic agent	R	Yes	Antecedent urologic surgery
82	1948	69 yrs.	M	0	P, St	—	—	Transient bacteremia	R	Yes	Antecedent urologic surgery
83	1948	60 yrs.	M	P	P, St, S	—	—	Etiologic agent	D	No	Antecedent surgery
84	1949	78 yrs.	M	0	P, St, S, T	0	—	Transient bacteremia	D	Yes	Antecedent urologic surgery
85	1956	73 yrs.	M	0	P, St, T, C	—	—	Etiologic agent	R	Yes	(A) Steroids for chronic leukopenia
86	1957	51 yrs.	M	0	St, C	—	—	Etiologic agent	R	Yes	(A) Steroids
87	1957	15 yrs.	M	P, St, T, C, Ery, Novo	P, C, E	—	—	Etiologic agent	R	Yes	(A) Steroids
88	1957	58 yrs.	M	P, St, T	P, St, T	—	—	Terminal bacteremia	D	No	Antecedent x-ray therapy to liver, N_2H, steroids (A)
89	1957	55 yrs.	F	T, S, Fur	P, St, T, C, S	0	—	Transient bacteremia	D	Yes	Multiple catheterizations of bladder
90	1959	70 yrs.	M	P, St	P, St	None	—	Terminal bacteremia	D	No	N_2H, x-ray (A)
91	1959	56 yrs.	M	—	P, St	Lung	Blood, lung, pleural fluid	Terminal bacteremia	D	No	—

endarteritis on a traumatic arteriovenous fistula. She subsequently developed endocarditis and died.[15] Despite rather serious illness, 10 patients survived the acute infection.

Clinical Manifestations: The urinary tract was the portal of entry in 10 episodes of bacteremia, cutaneous lesions were implicated in three patients, and the biliary tract, subphrenic abscess, and empyema were sources of bacteremia in one case each. In two patients, both of whom had received antecedent x-ray therapy and nitrogen mustards, no portal of entry could be demonstrated. Twelve patients underwent surgical procedures or instrumentation of the urinary tract just prior to development of bacteremia; four were receiving corticosteroids prior to the infection; and two had been given nitrogen mustards. Fever was a constant feature in this group except for terminal bacillemia in a moribund patient with Hodgkin's disease. Eleven patients had shaking chills, and shock was noted five times, twice in the absence of rigors. In one of these cases peripheral vascular collapse could have been due to a perforated peptic ulcer rather than sepsis. Jaundice without significant liver disease was seen in two patients.

Laboratory Data: Anemia was commented upon in only seven patients and could usually be accounted for by the underlying disease. As mentioned previously, leukopenia antedated sepsis and was not noted in association with bacteremia. Rather, leukocyte counts were elevated in 11 patients and within normal limits in two. Urine cultures were positive for *Pseudomonas* in 10 patients, and at the same time the organism was found in the surgical wound of one and in the sputum, pleural fluid, and subphrenic abscess of another. Four others had positive cultures for *Pseudomonas* from foci other than the blood (empyema, gall-bladder, throat, conjunctiva, and scrotum).

In two patients pseudomonas bacteremia occurred following blood stream infection with *Esch. coli* and enterococci (case 78) and *Staph. aureus* (case 87). In one patient *A. aerogenes* and enterococcus were cultured from the blood in addition to *Pseudomonas.*

The pattern of urethral instrumentation followed by bacilluria and bacteremia was common and occurred in nine patients.

One patient (case 83) had widespread invasion by *Pseudomonas,* with a subphrenic abscess, pneumonia, and pyelonephritis, from all of which *Pseudomonas* was cultured.

Treatment: Nine patients were receiving no chemotherapy at the time of bacteremia. Penicillin alone or in combination with sulfonamides or streptomycin was used six times, and three patients received multiple drugs. One patient (case 87) was being treated with six agents for staphylococcal sepsis when pseudomonas bacteremia supervened. As in previous groups, leukopenia, antecedent corticosteroids, and antimetabolites predisposed to pseudomonas sepsis; five patients, three of whom were receiving prophylactic antimicrobial therapy, fell into this category.

It is difficult to assess the role of antibiotics in this group of patients. In 10, bacteremia was a transient phenomenon, and four recovered without antimicrobial therapy. Of the six patients who did not survive, two were inadequately treated and four received optimal chemotherapy. This suggests that the outcome in transient pseudomonas sepsis is probably determined by the course of the underlying disease. In the remaining eight patients pseudomonas infection was deemed of primary importance in influencing the patient's course. In other words, although all patients in this group had significant associated disease, they would not have been hospitalized were it not for infection with *Pseudomonas.* Six of the eight recovered, five after receiving adequate treatment. The "inadequately treated patient" took sulfonamides, to which the organism may have been sensitive. Two patients died despite intensive therapy. Although the figures are small, they suggest that antimicrobials exerted a favorable action in a number of instances. One patient (case 81) with pseudomonas bacteremia and bacteriuria did not respond until polymyxin B was added to the antibiotic regimen. In another (case 78), antibiotics were ineffective until purulent exudate, containing *Pseudomonas,* was drained from the gall-bladder.

Pathology: Autopsies were performed in five of the eight patients who died during the course of infection. Three had no anatomic evidence of infection. One, a man with carcinoma of the lung (case 90) had a necrotizing tracheitis and bronchitis, and the patient with the arteriovenous fistula had diagnostic lesions involving the fistula, the aortic valve, and the endocardium of the left ventricle, and septic infarcts of the lungs and spleen. Cultures from these sites were positive for *Ps. aeruginosa.*

Significance of Pseudomonas Infection: As has been mentioned, in 10 of these patients pseudomonas bacteremia was transient and, in the six patients who died, it occurred within the last 48 hours of life—probably an agonal phenomenon. In the remaining eight it was responsible for two deaths—one postoperatively in a man with gastric ulcer, and the other in the patient with an infection at the site of an arteriovenous fistula.

Discussion

Ecology and Epidemiology: Pseudomonas bacteremia is most common at the extremes of life, the majority of cases occurring in infancy and old age. This is probably a reflection of the prevalence of prematurity, congenital abnormalities, and acute leukemia in infancy and childhood, and of debilitating diseases or urologic disorders in the geriatric age group. Of the 88 patients in this series, 27 were less than six months and 19 less than 12 years of age. Excluding the four adults with leukemia, 13 of the 16 adults were 50 years of age or older. Fraenkel described the increased susceptibility of small children to various types of pseudomonas infections.[16] Twenty-one of his 26 cases were less than two years old. Omphalitis as a

cause of fatal pseudomonas infection was emphasized by Wasserman.[17] Hand's five cases consisted of infants under 12 months.[18]

In a review of the literature, however, Kerby reported that more than 50% of the blood stream infections with *Pseudomonas* occurred in adults.[19] Among the 19 patients described by Keefer and Hewitt, there were only three children.[20]

Males are affected more often than females. This predilection is not apparent in the group of patients with hematologic disorders.

It was recognized many years ago that chronic disease, debility, infancy and prematurity, coexisting infections, and surgical procedures enhance the invasiveness of *Ps. aeruginosa.* The umbilical cord is the most important locus of pseudomonas infection in early infancy. Omphalitis may be inapparent clinically but microscopic examination frequently reveals the avascular lesions in the cord.[17] In several older communications, it was reported that the classical skin lesions of *Pseudomonas,* ecthyma gangrenosum, were often a sequel to acute exanthemata, such as rubeola or scarlet fever.[21-23] Systemic pseudomonas infection may follow otitis media in children, and congenital anomalies are also known to predispose to infection. Pseudomonas meningitis has previously been reported in association with meningomyelocele,[24] and pneumonitis and bronchiolitis with this organism commonly complicate mucoviscidosis.[25] A wide variety of other developmental errors has also been noted.[26] In general, this study substantiates the role of *Ps. aeruginosa* as a primary pathogen in man. Infection with it is almost invariably associated with diminished resistance in the host and occurs in an environment favorable to infection—the hospital.

Six children presented with diarrhea of varying duration and severity. The role of *Pseudomonas* in the pathogenesis of diarrhea has been reviewed by Florman,[27] Finkelstein,[28] and Schaffer and Oppenheimer.[13] Some children with pseudomonas diarrhea have the pathognomonic necrotic ulcers in the bowel, which are as specific as are the gangrenous skin lesions.[28, 29] Others, however, with the same illness and positive stool and blood cultures, have no intestinal lesions at autopsy. The available data do not clarify the pathogenesis of the infection in these patients. However, most of these patients had received antimicrobials prior to appearance of *Pseudomonas* in the stool, suggesting that these drugs may play an important role in the etiology of pseudomonas enterocolitis, much as in staphylococcal enteritis. Experimentally, massive antibiotic feeding to chinchillas was frequently followed by pseudomonas enteritis.[30] Finally, epidemic diarrhea may be caused by this organism but the specific factors favoring its development are obscure.[31]

The role of antileukemic drugs and steroids in facilitating invasion by *Pseudomonas* is difficult to define. These drugs are known to alter host resistance, but the diseases in which they were employed are known to predispose to infection even in the absence of steroids. The basic defect

in host resistance in patients who have leukemia remains poorly defined. Suffice it to say that many factors, including prolonged hospitalization, leukopenia, inhibition of the local inflammatory response by corticosteroids, and prophylactic antibiotics favor the parasite. In such a climate the threat of bacterial infection rises, and while the staphylococcus may be the initial invader, *Pseudomonas* frequently overwhelms the host's last line of defense. It seems difficult to attribute this infection to leukemia per se, in the face of the marked increase in the incidence of pseudomonas bacteremia. In the first 10 years of this study only three patients with leukemia had pseudomonas bacteremia. Twenty-five bouts of sepsis have been observed since 1950 when broad spectrum antibiotics, adrenal hormones, and antimetabolites came into greater use. In these 25 bouts of pseudomonas bacteremia, antimicrobial therapy antedated blood stream invasion in 23 instances, and antileukemic drugs and steroids were each in use 17 times prior to the appearance of sepsis. Whether these agents increased the vulnerability of the host or whether they merely prolonged life sufficiently for infection to set in remains a moot point.

There is good evidence that the incidence of pseudomonas bacteremia has increased not only in patients with leukemia but in other groups as well, particularly premature infants. In general, twice as many infections per 1,000 admissions occurred between 1950 and 1959 than in the preceding decade. It is also of interest that during certain years most or all of the cases occurred in only one group. For example, in 1945 all cases were confined to children; in 1950, five of eight bouts occurred in patients with leukemia; in 1951, all four cases were seen in prematures. Unfortunately, serologic or bacteriophagic typing of these strains was not carried out; the chronologic pattern, however, suggests that these infections were not only nosocomial but that they were transmitted from one patient to another either directly or via asymptomatic carriers. Transmission of *Pseudomonas* from one patient to another via asymptomatic human carriers has been demonstrated in urologic wards.[32]

Clinical Considerations: All but a few of our patients had some serious disease predisposing to bacteremia. The so-called "typhoid form," which is characterized by fever, malaise, myalgia, and diarrhea and occurs predominantly in the tropics, was not observed. This illness, which is also called "thirteen-day fever" or "Shanghai fever," is self-limited and has a good prognosis. It is thought to be transmitted by the enteric route.[33, 34] Three children in our group (cases 23, 29, 33) may have had this form of pseudomonas infection. The fact that only one recovered may be attributed to the severe water and electrolyte imbalance which accompanied the diarrhea.

The skin lesions classically associated with generalized pseudomonas infection, ecthyma gangrenosum, begin as red macules which become pustular and then proceed to hemorrhagic necrosis. They are usually

multiple and are most often noted in the axillary and anogenital regions. Fraenkel considered them pathognomonic of pseudomonas infection and reported their presence in 15 of 26 cases.[16] Markley et al. observed a high incidence of these lesions in the Peru burn project.[35] The initial vesicle usually appeared at the site of injury, but subsequent lesions involved normal skin. Death followed within 24 to 48 hours and characteristic visceral lesions were found at autopsy. The relative dearth of cutaneous manifestations in our study may be due to differences in the basic diseases predisposing to infection. It is also conceivable that skin eruptions were attributed to other causes.

The pyrexia usually associated with gram-negative bacteremia is a very inconstant feature in young children. Four of 14 full-term infants and 13 of 16 prematures remained afebrile. Older children and adults almost always had hectic fevers. Silver and his associates recently examined the

TABLE 5

Bacteremia with Other Organisms in 11 Leukemic Patients and 11 Nonleukemic Patients with Pseudomonas Bacteremia*

	Preceded		Concurrent		Subsequent		Total
	L	NL	L	NL	L	NL	
Staphylococci	6	4	0	0	0	1	11
Enterococci	1	2	0	2	1	0	6
Coliform	2	3	1	4	1	0	11
Other	2	0	1	0	0	1	4
Total	11	9	2	6	2	2	32

* Legends: L = Leukemia; NL = No leukemia.

significance of fever as an index of infection in patients with acute leukemia.[36] Their patients were febrile for almost one-half the time spent in the hospital, and of 92 episodes of fever, 59 were related to infection. Forty-four of these were of bacterial etiology, and bacteremia occurred in 14 with seven deaths.

Leukopenia is thought by some to be a frequent manifestation of pseudomonas sepsis.[21, 37] This was not observed in our patients unless it antedated infection. Exclusive of these patients and others with leukemia, 10 had leukocyte counts above 20,000/cu. mm., six above 15,000, eight above 10,000, and five above 5,000. Leukopenia was observed in only one patient.

Bacteremia with organisms other than *Pseudomonas* occurred in 22 patients, 11 of whom had leukemia (Table 5). There were 27 bouts of mixed bacteremia in all. Seventeen preceded infection with *Pseudomonas,* seven occurred concurrently, and three subsequently. Staphylococci and coliform bacteria were cultured in 11 instances each and enterococci were isolated six times. Three patients with mixed bacteremia recovered completely. Diphtheroids were cultured from the blood in two patients with blood dyscrasias. This agrees with the experience of Fleisher.[38] Kassel

has challenged the interpretation of these observations and argues that diphtheroids in blood cultures invariably represent contamination.[39]

The clinical picture of pseudomonas bacteremia in adults without leukemia is typical of blood stream infection with other bacterial species.[40] Hectic fevers, true rigors, and leukocytosis were present in most patients and shock was seen in four of them. Nine had had surgical procedures usually involving the lower urinary tract just prior to bacteremia and two had undergone bladder catheterization. Barrington has noted that transuretheral resection, in particular, is associated with a high incidence of bacteremia.[41] The prognosis in these patients is much better than in patients with severe debilitating diseases. In fact, institution of adequate drainage alone controlled some of these infections in the absence of specific antibiotics. Routine antimicrobial chemoprophylaxis in urologic surgery is fruitless and does not prevent bacteremia. In any event, the sanguine prognosis provides a further argument against it.[42, 43]

Pathology: An attempt was made to evaluate the etiologic role of *Pseudomonas* in the patients. The presence of typical necrotic nonexudative lesions associated with thrombosis of neighboring vessels was accepted as definite evidence of tissue invasion by the organism. In the absence of these specific morphologic changes, positive post-mortem cultures or organisms in sections stained for bacteria were also considered pathologic evidence of generalized pseudomonas infection. One or both of these criteria were fulfilled in 75% of autopsies. Of the 12 patients without definite anatomic evidence of pseudomonas sepsis, blood cultures had become negative prior to death in eight. In four premature infants post-mortem blood cultures constituted the only evidence of bacteremia which may well have been a terminal event. All patients who recovered or who had no autopsy had adequate proof of systemic infection with *Ps. aeruginosa.*

Relationship of Antimicrobial Therapy to Infection by Pseudomonas: Prior to pseudomonas infection most patients had been receiving one or more antibiotics either for prophylaxis or for treatment of another infection. Table 4 details the status of drug therapy before and after the onset of pseudomonas bacteremia.

Thirty-two patients did not receive antibiotics prior to pseudomonas sepsis. In 13 of these, 32 bacteriologic cures associated with some clinical improvement were obtained. However, many of these patients subsequently died of their primary disease. Fifty-nine patients developed bacteremia while receiving antimicrobial drugs and 14 of these responded to therapy. Twenty-two of these 59 were being treated for bacteremia due to another organism, but in 37 the indications for antibiotics were poorly defined as incipient or suspected infection, prematurity, or coverage during surgery.

The efficacy of routine administration of antibiotics to premature infants has been questioned and may, in fact, predispose to superinfection by *Ps. aeruginosa.* These drugs are also given to prevent the pulmonary com-

plications of mucoviscidosis.[44, 45] Garrard has described superinfections with *Pseudomonas* in four infants on his regimen.[46] Others have found that *Pseudomonas* may appear in the flora of the respiratory tract during therapy but that it infrequently causes infections.[44] One of the three cases of mucoviscidosis in this series was receiving antibiotic prophylaxis.

Unfortunately there are no well controlled studies of chemoprophylaxis in patients with mucoviscidosis and leukemia or in premature infants. There is ample evidence that antimicrobials do not prevent urinary tract infections in patients with indwelling urethral catheters.[47, 48] Furthermore, drug-resistant organisms are much more likely to appear in the urine of treated patients. Similarly, the incidence of bacteremia after urologic procedures is not reduced by preoperative antibiotics.[42, 43] Howe [49] has emphasized that routine use of antibiotics after surgery predisposes to superinfection with resistant organisms. Weinstein has condemned the use of chemoprophylaxis in general [50] and in viral infections in particular.[51] Certainly, attempts to prevent bacterial endocarditis following surgical manipulation in patients with valvular heart disease is a valid indication for prophylactic therapy, but even here it is evident that the effort is not always successful.

Patients who did not receive antecedent chemotherapy had a slightly higher rate of bacteriologic cure (40%) than those who were treated prior to infection (23%). Again, this may reflect the severity of the underlying disease more than the deleterious effect of the drugs. However, it appears likely that emergence of *Pseudomonas* as a pathogen was facilitated by the alteration of the microbial flora by antibiotics.

Although 27 patients responded to treatment of bacteremia, 12 died within several months, two following a second infection with this organism. In the leukemic patients hematologic remission paralleled bacteriologic cure. Improvement in the blood picture tended to be associated with enhanced resistance to infection and vice versa.

A variety of antibiotics alone or in combination was used (Table 6). Polymyxin B was employed in 12 instances with five cures. Three patients in whom this drug was ineffective received it for only one day prior to death. The best results were obtained when polymyxin B was used in combination with streptomycin. Four of the five successfully treated cases had failed to respond to other drugs. Streptomycin was employed in combination with another agent in 18 of the 27 patients whose blood stream was sterilized and appears to be of some value in this infection. However, 22 patients received streptomycin without improvement. Tetracycline and/or chloramphenicol was administered to 31 patients with a favorable response in 13, nine of whom also received streptomycin or polymyxin, or both. In general, several drugs were given to each patient. Penicillin was used frequently and 49 patients received it prior to pseudomonas infection. Among 84 patients who were treated for pseudomonas bacteremia, penicillin was part

of the regimen in all but 11. The rate of cure in this group was less than 10%. It appears, therefore, that penicillin in ordinary dosage probably has no place in the treatment of pseudomonas infection.

As has been mentioned, the endogenous defense mechanisms of the host are probably the most important determinant of the outcome in pseudomonas sepsis. However, there is little doubt that the combination of polymyxin B and streptomycin is of considerable value in pseudomonas bacteremia.

TABLE 6

Relationship of Antimicrobial Drugs to Pseudomonas Bacteremia

Therapy	Prophylaxis									Total
	None	Pen.	Pen. and Strep.	Sulfa	Pen. and Sulfa	Pen., Strep., Sulfa	B. S.	Pen. and B. S.	Pen., Strep., B. S.	
None	2/7									2/7
Pen.	0/2	0/4			0/1					0/7
Pen. and Strep.	1/3	1/1	0/7							2/11
Sulfa	1/1			1/1						2/2
Pen. and Sulfa	0/1	0/2			0/4					0/7
Pen., Strep., Sulfa	2/3	0/1	1/1			0/1				3/6
B. S.	2/3		0/1				0/2	0/2		2/8
Pen. and B. S.			0/1					0/5	1/1	1/7
Pen., Strep., B. S.	3/6	1/2	0/2				2/3		0/3	6/16
PX	1/3	1/2	1/1				0/3		2/3	5/12*†
Others	1/3	0/1					1/1	2/3		4/8*
Total	13/32	3/13	2/13	1/1	0/5	0/1	3/9	2/10	3/7	27/91

The top of the vertical column lists the drug used prior to pseudomonas infection. The column at the extreme left of the vertical line notes the drug used in therapy. The numerator records the number of bacteriologic cures, while the denominator connotes the total number of patients on a regimen.

* 7 of the 9 bacteriologic cures in these groups also received streptomycin.

† 3 of the failures on polymyxin received the drug for only one day.

B. S. = Broad spectrum drugs (tetracyclines and chloramphenicol).

PX = Polymyxin B.

Topical application of polymyxin B in burns, wound infections, and otitis media is attended by minimal side reactions. In meningitis this drug is effective intrathecally, and it has also been administered orally to treat diarrhea associated with positive pseudomonas stool cultures. Bacteremia requires parenteral administration of the drug, which in its present purified form is considerably less nephrotoxic than were earlier preparations. Pain at the site of injection and dysesthesias are troublesome side effects.[52] A new analog of polymyxin B, Colistin, is relatively free of these side effects.[53]

Spontaneous recoveries from pseudomonas bacteremia do occur, usually in the "typhoidal" form or following transient bacteremia after urologic instrumentation. Nevertheless, the intelligent use of antibiotics, particularly polymyxin B, Colistin, streptomycin, and in certain instances the broad spectrum drugs or kanamycin, may improve the prognosis in this frequently fatal infection.

Summary and Conclusions

The records of 88 patients who had had 91 bouts of pseudomonas bacteremia were studied. Eighteen of these occurred in premature infants, 27 among children with congenital abnormalities or severe acquired diseases such as nephrosis, 28 in children and adults with blood dyscrasias, and 18 in adults with a variety of illnesses, frequently following urologic instrumentation. Forty-six patients were less than 12 years old and males predominated, particularly in the group of premature infants and in the elderly adults.

The prognosis was poor and there were only 15 survivors. Bacteremia was successfully treated in 12 additional cases but death occurred due to associated disease. In general, the associated disease state was the most important single factor affecting the outcome.

The clinical picture was not characteristic, and in adults resembled any bacteremia. Among infants, fever was unusual. Ecthyma gangrenosum is diagnostic of pseudomonas septicemia but was found only in one patient in this group. Leukopenia was usually associated with leukemia or antedated the infection.

Blood stream invasion by *Pseudomonas* occurred most often in patients receiving prophylactic antibiotics, and in 22 instances it developed as a superinfection, frequently following staphylococcal bacteremia. Pseudomonas infections are rarely seen in patients at the time of hospitalization and are almost always nosocomial. Certain clues should increase the suspicion of pseudomonas septicemia:

1. Infection of the umbilical stump or of the skin in premature infants.
2. Sudden deterioration in the status of children with nephrosis or mucoviscidosis.
3. Leukemic patients who, during the acute stage with leukopenia, are receiving antimicrobials, steroids, and folic acid antagonists.
4. Patients undergoing therapy for serious staphylococcal or coliform infections in whom a worsening in the clinical picture after initial improvement suggests that a superinfection with *Pseudomonas* might be present.

Response to treatment is variable and depends to a large extent upon the underlying disease. Polymyxin B was the most effective antibiotic and should be given in conjunction with streptomycin. Adequate drainage was as necessary in sepsis with *Pseudomonas* as in any other infection.

Morphologic confirmation of the pathogenicity of this organism was obtained in 75% of the 55 autopsied cases.

Summario in Interlingua

Esseva studiate le protocollos de 88 patientes qui habeva 91 episodios de bacteremia per pseudomonas. Dece-octo del casos occurreva in infantes prematur, 27 in juvenes con congenite anormalitates o sever morbos acquirite (como per exemplo nephrosis), 28 in juvenes e adultos con dyscrasias del sanguine, e 18 in adultos con un varietate de morbos, frequentemente occurrente como sequella de instrumentation urologic. Quaranta-sex del patientes habeva minus que 12 annos de etate. Le masculos predominava, specialmente inter le infantes e le patientes de etates avantiate.

Le prognose esseva mal. Le total del superviventes esseva solmente 15. In 12 casos (in ultra del 15), le bacteremia esseva tractate a bon successo, sed morte superveniva causate per un morbo associate. A generalmente parlar, le typo de morbo associate esseva le plus importante factor individual in le determination del resultato.

Le tableau clinic non esseva characteristic. In le adultos, illo resimilava non importa qual altere bacteremia. Inter le infantes, febre esseva inusual. Ecthyma gangrenose es diagnostic pro septicemia a pseudomonas, sed in le presente gruppo illo esseva constatate in un caso solmente. Leucopenia esseva associate usualmente con leucemia o precedeva le infection.

Invasion del circulation sanguinee per pseudomonas occurreva le plus frequentemente in patientes sub prophylaxe a antibioticos. In 22 casos illo se disveloppava como un superinfecion, frequentemente post bacteremia staphylococcal. Infectiones per pseudomas es vidite rarmente in patientes arrivante al hospital; illos es nosocomial in quasi omne casos.

Le responsa al tractamento esseva variabile e dependeva in grande mesura del morbo subjacente. Polymyxina B esseva le antibiotico le plus efficace e deberea esser administrate in conjunction con streptomycina. Adequatia de drainage esseva tanto necessari in sepse per pseudomonas como in non importa qual altere typo de infection.

Confirmationes morphologic del pathogenicitate de iste organismo esseva obtenite in 75% del 55 necropsias.

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FAMILIAL RENAL TUBULAR ACIDOSIS *

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ACIDOSIS of renal origin is an increased hydrogen ion concentration due to an impairment in the excretion of titratable acid and/or ammonium ion, to an excessive excretion of bicarbonate, or to a combination of these two defects.[1-4] While all renal acidosis is presumably tubular in origin, the term "renal tubular acidosis" has come to represent (and will be so used in this text) that syndrome characterized by a hyperchloremic acidosis resulting from marked impairment in the ability to excrete an acid urine.[3-15] The latter is significantly out of proportion to any impairment in glomerular filtration, and hence is not associated with azotemia or "contracted kidneys." While this type of renal acidosis may be found in various disease states (pyelonephritis, nephrocalcinosis) and metabolic disorders (Fanconi's syndrome, Lowe's syndrome, Wilson's disease, galactosemia, nephrogenic diabetes insipidus)[3, 5, 15-24] the present report is concerned primarily with that form of renal acidosis referred to as "late primary renal tubular acidosis." [15] This implies the absence of the aforementioned metabolic disorders, persistence of the condition into adult life, and the absence of any pronounced azotemia despite the presence of nephrocalcinosis and pyelonephritis which occur frequently in this disorder.

The etiology of this type of renal tubular acidosis is unknown. Previous reports have suggested that the basic defect in renal tubular function is governed by a genetic factor,[15, 25, 32] but conclusive evidence has been lacking. This report presents the findings in a family in which at least seven members have renal tubular acidosis with nephrocalcinosis. These data now represent the strongest reported evidence that a genetic factor is operative in this disorder and, furthermore, that this factor is autosomal and dominant.

RESULTS

Familial Characteristics: The proposita of the present study (patient III 5) presented initially with pyelonephritis at the age of three and was

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TABLE 1
Clinical and Serum Data in Patients of the Present Study

Patient	Age	Sex	Treatment	Nephrocalcinosis & Nephrolithiasis	Stone Composition	Pyelonephritis	Fatigue, Weakness	Tetany	Rickets, Osteomalacia	Serum										
										Na mEq./L.	K mEq./L.	CO_2 mM./L.	Cl mEq./L.	Cr mg.%	NPN mg.%	Ca mg.%	P mg.%	Alk. P'tase Units§	Uric acid mg.%	Blood pH
I 2	d. 75	F	None	3+		1+	1+	0	0	133	3.8	15	110	4.1	60	8.3	4.3			
II 5	57	F	None	2+		1+	0	0	0	146	3.8	16	119	1.5					6.4	
II 6	55	M	None	0		0	0	0	0	134	4.5	27	105		12	9.6	3.0	1.9 B.U.		
II 7	53	F	None	0		0	0	0	0	130	5.5	25	108							
II 8	46	M	None	3+	$CaPO_4$	0	0	0	0	144	4.0	16	118	2.1		9.8	4.9	5.4 B.U.		
			NH_4Cl, day 3	3+	$MgPO_4$	0	1+	0	0	142	4.1	11	120	2.0						
II 4	35	F	None	1+		0	0	0	0	147	4.2	22	105			9.5	3.3	6.9 K.A.U.		
III 5	3	F	None	?		0		0	1+											
	4		None	2+	$CaPO_4$	0		0	1+											
	7		None	2+		1+	1+	0	1+			16	103	1.5	45	10.4	4.4	17.0 B.U.		
	22		None	3+	$CaPO_4$	1+	1+	0	0	140	4.5	21	111	1.0		9.8	4.0	5.0 B.U.	2.0	
	22		NH_4Cl, day 3	3+		1+	3+	0	0			16	117							
	22		Na Citrate‡	3+		1+	1+	0	0	140	4.4	26	108							
III 6	20	F	None	0		0	0	0	0	137	4.0	25	103	1.0		10.0	3.5	2.0 B.U.		
	20		NH_4Cl, day 3	*			1+			140	4.0	21	110							
III 7	11	M	None	3+	$CaPO_4$	0	0	0	0	135	3.0	15	110	1.3	40	9.8	3.8	5.0 B.U.	3.1	
	18		None	3+		0	0	0	0	144	3.4	20	116	1.6	47	11.3	4.0	7.0 B.U.	5.7	7.33
	18		NH_4Cl, day 3	3+	†	0	1+	0	0			16	119							
	18		Na Citrate‡	3+		0	0	0	0			28	110							
III 8	10	M	None	1+		0	0	0	0											
	16		None	1+		0	0	0	0	138	4.2	23	108	1.1		10.4	5.8	4.8 SJR U.		
	16		NH_4Cl, day 3	1+		0	1+	0	0			18	110							
IV 8	1 mo.	M		0	0	0	0	0	0	139	4.7	22	106			10.6	7.6	8 B.U.		
			NH_4Cl, day 4	0	0	0	0	0	0	139	3.6	11	118							

* Light microscopy of renal biopsy tissue (percutaneous, needle) revealed no significant abnormalities.
† Stone analysis: multiple stones with concentric laminae of cryptocrystalline calcium hydrogen phosphate dihydrate.
‡ Data obtained following several weeks of oral Na citrate therapy.
§ Alkaline phosphatase units: B. U., Bodansky units; K. A. U., King-Armstrong units; SJR U., Shinowara-Jones-Reinhardt units.

found to have marked nephrocalcinosis and nephrolithiasis. The discovery of nephrocalcinosis in the patient's father and two brothers was reported in 1955 by Pitts, Schulte, and Smith [30] although the significance and extent of the renal acidosis was not appreciated at that time. Recent demonstration of renal tubular acidosis in the proposita (III 5) led to the present study in which all members of this family were investigated and seven were

TABLE 2

Urine Data in Patients of this Study

Patient	Age	Sex	Treatment	Urine										
									24 Hours					
				pH	Max. S.G.*	15 min. PSP	C_{cr} ml./min.	Glucose	Amino acids	Titratable Acid mEq.†	NH_4 mEq.†	Ca mg.	P mg.	Aldosterone† µg.
I 2	d. 75	F	None	7.0	1.009			0						
II 5	57	F	None	6.5	1.008			0		13				3.0
II 6	55	M	None	5.5	1.025			0						
II 7	53	F	None	5.7	1.020			0						
II 8	46	M	None NH_4Cl, day 3	7.0 6.3	1.010	15%		0	Normal	9 12				5.7
III 4	35	F	None	7.0	1.011			0						
III 5	3 4 7 22 22 22	F	None None None None NH_4Cl, day 3 Na Citrate	6.5 7.5 6.0 7.5	1.012 1.011	30% 25%	90	0 0 0 0	Normal	11 12		40‡ 205 400 40	812‡	
III 6	20 20	F	None NH_4Cl, day 3	5.5 4.3	1.024	32%	135	0	Normal	13 33	13 109	65	950	
III 7	11 18 18 18	M	None None NH_4Cl, day 3 Na Citrate	7.5 7.5 7.0 7.5	1.010 1.010	22%	85 25	0 0	Normal	8 14	17 50	207 410 90	865	
III 8	10 16 16	M	None None NH_4Cl, day 3	6.5 5.7	1.012	30%		0	Normal	12 17				3.0
IV 8	1 mo.	M	NH_4Cl, day 4	7.0 6.5	1.023			0	Normal	0.4 2.8	3.2 6.3			

* Specific gravity following 18 hours of dehydration and Pitressin administration.[31]
† Approximate normal control values: titratable acidity, 18 mEq./24 hr., ammonium, 24 mEq./24 hr.,[9,13] and aldosterone, 3 to 13 µg.%/24 hr. For reported values during ammonium chloride loads see references.[9,13,31]
‡ Balance study at this time over a six-day period demonstrated a zero balance for calcium and a −0.6 gm. negative balance for phosphate per day.

shown to have renal tubular acidosis. Figure 1 portrays the occurrence of renal tubular acidosis in this family and in those families previously reported in the literature.[25-32] The significant laboratory and clinical data in nine members of the family presented here are recorded in Tables 1 and 2. No consanguineous marriages were involved.

Laboratory Findings: The individuals with hyperchloremic acidosis all had nephrocalcinosis of varying degrees visible in roentgenograms of the abdomen (Figure 2). These individuals have all passed numerous renal

calculi which were composed principally of calcium phosphate. Isosthenuria was a uniform finding despite dehydration and the injection of Pitressin.[33] Rickets, muscle weakness, excessive fatigue, and hypokalemia were uncommon and hypophosphatemia was not observed. Significant azotemia was recorded in only one member (I 2) during her terminal illness. While

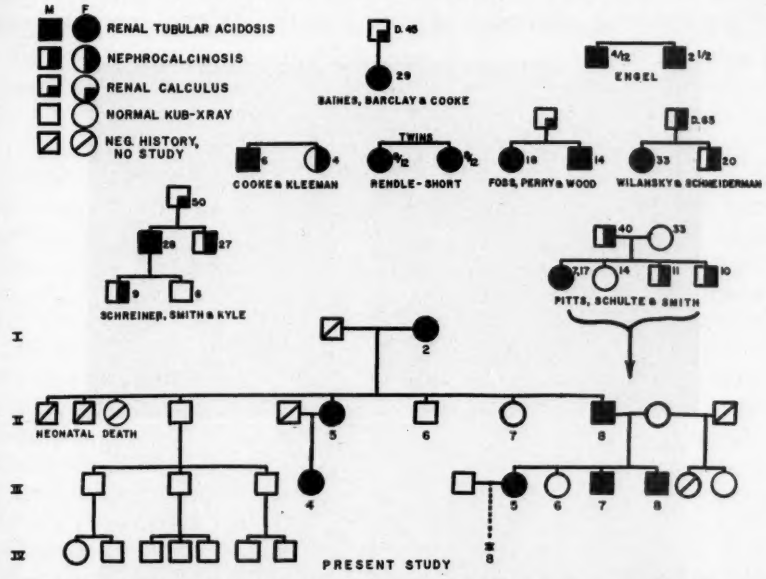


FIG. 1. Familial occurrence of renal tubular acidosis in previous reports[25-32] and in the present study. The numbers adjacent to the symbols in the upper half of the chart represent the age of the individuals at the time of study. In the present study: (1) The roman numerals at the left designate the generations, and the numbers below the symbols designate the individuals in each generation for presentation of their clinical data in Table 1; (2) The open symbol for "normal" signifies in each instance a normal roentgenogram of the abdomen, a normal serum chloride (101 to 106 mEq./L.), and an acid urine (pH 5.0 or less). All of the individuals represented here as having renal tubular acidosis have also had nephrocalcinosis. The place of individuals in this family previously reported by Pitts, Schulte, and Smith,[30] members II 8, III 5, III 6, III 7, and III 8 of the present study, is indicated by the bracket and arrow. A recheck of the previous hospital records of these individuals allowed correction (Table 1) of certain errors in the previous reporting of their clinical data.[30]

earlier data were not available in this individual, numerous observations over a two-month period confirmed the presence of a persistent hyperchloremic acidosis with alkaline urines. Autopsy examination disclosed extensive nephrocalcinosis and moderate pyelonephritis.

Urine Values: All urines from the individuals with acidosis had pH values greater than 6.5 during the ingestion of regular diets, and none had

*IV 8: Data in this newborn male at one month of age are listed in Tables 1 and 2 and discussed in the text.

less than pH 5.7 (5.7, 6.0, 6.3, and 7.0) following acid challenge (oral ammonium chloride, 2 mEq./Kg. of body weight per day for three days). The urinary excretion of titratable acid was reduced in five of these individuals and failed to increase significantly in the four who were given ammonium chloride. The nonacidotic sibling (III 6) of the proposita (III 5) excreted low amounts of titratable acid and ammonium while on a normal diet, but following ammonium chloride ingestion excreted amounts com-

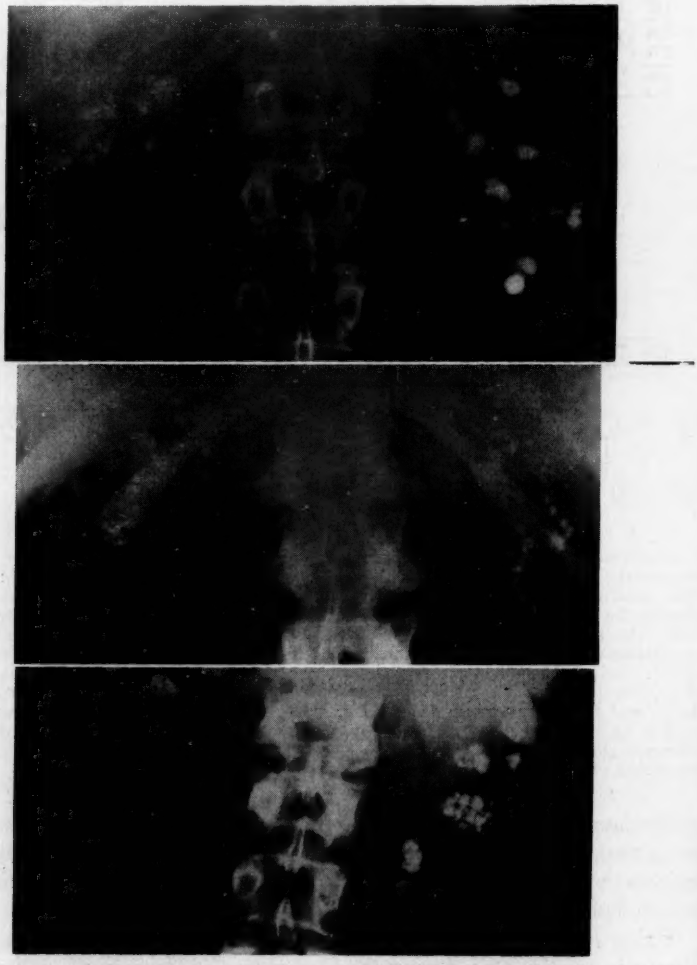


FIG. 2. Roentgenograms of the renal areas of patients II 8, III 5, and III 7 (from above downward) demonstrating pronounced bilateral nephrocalcinosis and nephrolithiasis. Nephrocalcinosis in the other affected members was less extensive and less suitable for demonstration.

parable to those of normal individuals.[5, 9] Ammonium excretion, measured in only one other acidotic member (III 7), was found to be slightly low with a less-than-normal increase following ammonium chloride. These values, however, were not significantly reduced relative to the urine pH.[2, 3, 8, 9] Glycosuria and aminoaciduria were not observed in the individuals studied and normal values were obtained for the daily urinary excretion of aldosterone * in three acidotic members. Mild hypercalciuria recorded in two others (III 5, III 7) increased following ammonium chloride ingestion and disappeared following correction of the acidosis.†

Comments

The data presented here suggest that renal tubular acidosis is a disorder in which the basic mechanism (limitation in the renal ability to excrete acid) is governed by an autosomal dominant gene. Its occurrence in three and probably four consecutive generations of the family studied (Figure 1), the 1:1 ratio of affected to nonaffected siblings, and the apparent transmission from father (II 8) to one of two daughters (III 5) and to two sons III 7, III 8) are findings consistent with this conclusion. The number of individuals in this study is too small to allow definite conclusions regarding the degree of penetrance of the genetic factor. While all affected members showed both acidosis and nephrocalcinosis, the severity of these manifestations was variable. It cannot be concluded, however, that this variability relates to varying expressivity of a genetic factor since numerous other factors (e.g., secondary pyelonephritis) could obviously affect the severity of these manifestations. No instance of nephrocalcinosis without acidosis (the "incomplete syndrome of renal tubular acidosis," as described by Wrong and Davies,[3]) was observed, although the hyperchloremic acidosis in patients III 4 and III 8 was minimal. An attempt to uncover a clinically inapparent (lesser) impairment in hydrogen ion excretion was attempted in one instance by the administration of an acid load to the normal sibling III 6. Low control values for ammonium and titratable acid excretion, perhaps due to low dietary loads of hydrogen ion, increased to values comparable to those of normal individuals following acid challenge,[8, 9] and the urine became significantly acid. Lesser degrees of expressivity, therefore, exhibited as mild acidosis without nephrocalcinosis, or as nephrocalcinosis without acidosis, or merely as impaired excretion of an acid load without either of the other manifestations, could not be documented in this family.

The data in the newborn child (IV 8) are inadequate to draw many conclusions at the present time. The slightly reduced carbon dioxide content of the serum during normal conditions, and the persistence of an alkaline urine during the ingestion of acidifying loads of ammonium chloride, sug-

* Kindly performed by Dr. Edward G. Biglieri, University of California School of Medicine, San Francisco, Calif.

† Acidosis was corrected by the oral administration of approximately 120 ml./day of a solution containing 100 gm. of sodium citrate and 50 gm. of citric acid/L. of water.

gest that this child might be affected at this time. Data in newborn infants for the response to ammonium chloride are difficult to locate. The urine titratable acidity in the child IV 8, although increasing sevenfold following the ingestion of ammonium chloride, was generally lower than those values reported by Gordon, McNamara, and Benjamin for full term infants.[34] The fall in serum bicarbonate and the rise in the serum chloride were somewhat greater than normal, and the failure to acidify the urine was distinctly unusual for a child of this age.

Data from previous reports [25-32] are consistent with the presence of an etiologic genetic factor in this disorder. It should be appreciated that in some of these reports, the failure to demonstrate acidosis in certain individuals with nephrocalcinosis or renal calculi (Figure 1) and the failure to detect abnormalities in other relatives might have been due to the lack of study rather than to the absence of such abnormalities.* Huth, Webster, and Elkinton have recently reviewed the data from these reports and have likewise concluded that an autosomal dominant genetic factor is probably involved.[15] If this is indeed the case, then renal tubular acidosis might be considered an "inborn error of metabolism" whose defect in renal tubular function is governed by the lack of or alteration in some specific enzyme system or systems within the renal tubule.[14, 35, 36] The explanation of the underlying physiologic defect must obviously await further studies.

The likelihood that a genetic factor determines the occurrence of renal tubular acidosis makes apparent the need to seek this disorder in the relatives of affected individuals. Discovery of this disorder early in its course and the institution of proper medical management are necessary if the complications of renal calcification, pyelonephritis, osteomalacia, and potassium depletion [11, 12, 37-40] are to be prevented.

Summary

Study of a family in which at least seven members have renal tubular acidosis suggests that the underlying defect in renal tubular function is determined by an autosomal dominant gene.

Summario in Interlingua

Esseva studiate un familia in que al minus septe membros habeva acidosis renotubular con nephrocalcinosis. Iste datos representa nunc le plus forte evidentia reportate que le defecto subjacente in iste disordine es governate per un gen dominante autosomal. Tal datos rende apparente le desiderato de cercar le disordine in consanguineos de subjectos afficite. Le discoperta precoce e le institution del appropriate mesuras medical es necessari si le complicationes de calcification renal, de pyelonephritis, de osteomalacia, e de depletion de kalium debe esser prevenite.

* Incomplete data suggest that the father in the report by Foss, Perry, and Wood [31] and the 50-year-old father, the 27-year-old brother, the 9-year-old son with nephrocalcinosis, and the 24-year-old sister in the report by Schreiner, Smith, and Kyle [29] might have been acidotic.

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A COMPARATIVE STUDY OF VASCULAR RESPONSES TO THE INTRA-ARTERIAL AND INTRAVENOUS ADMINISTRATION OF VARIOUS VASODILATOR AGENTS *†

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THE management of an occlusion of an artery to an extremity has remained a major problem in spite of certain advances made in this field. Several technics for restoration of primary circulation by surgical means to a limb which has lost its mainline arterial supply have been developed. Technics available at present are arteriectomy with insertion of a graft,[1] bypass without arteriectomy,[2] endarteriectomy,[3] and various modifications of these procedures. Since there are limitations to the applicability and ultimate efficiency of these surgical methods,[4-7] efforts to promote the development of collateral circulation have continued. Surgical methods designed to enhance collateral circulation include arteriectomy without grafting [8, 9] and sympathectomy.[10] Local blocking of the regional paravertebral ganglia [11] is equivalent to temporary reversible sympathectomy. The merits as well as the limitations of these methods have been widely discussed in the literature [12, 13] and need not be repeated here. In addition, a search continues for drugs which would, by various mechanisms, be capable of enhancing collateral circulation in limbs totally or partially deprived of their primary arterial blood supply.

Evaluation of the effectiveness of drugs is difficult in the chronic as well as in the acute stages of occlusive arterial disease.[14] Evaluation of improvement of chronic arterial insufficiency which may occur with or without therapy, and which is always slow, calls for critical clinical observation. Evaluation of methods of therapy designed to deal with acute arterial occlusion in an extremity is also difficult due to prognostic uncertainties. Where conditions warrant aortography, sufficient visualization of collateral channels may be obtained as a helpful prognostic aid. The prognosis of acute arterial occlusions occurring in patients who have been on long-term periods of oral administration of agents interfering with the action or the

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formation of catecholamines is in our experience more favorable than in those not receiving such drugs.

Most of the clinical studies reported in the literature have not been well controlled,[13-15] but two interesting reports [16, 17] have dealt with the intra-arterial administration of various agents. We decided, therefore, to attempt to clarify some of the problems by ascertaining the vascular responses to

TABLE 1

Vascular Responses to Nine Vasodilator Agents

Generic Name	Commercial Name	Dose Used	Pharmacologic Classification	Action on Peripheral Blood Flow	Side Effects
Nylidrin hydrochloride	Arlidin	7 mg.	Adrenalin-like substance	Marked increase in blood flow to muscle; small increments in skin flow	Extrasystoles, tachycardia
Diethylamino ethanol		50 ml.	Amino alcohol	Increase in total flow; skin temperature: marked rise in glomus areas, inconsistent in blush areas	"High" feeling, occasional nausea and vomiting
Chlorison amine	Ecolid	3 mg.	Ganglionic blocker	Marked increase in total blood flow (skin and muscle)	Postural hypotension, constipation, blurring of vision
Histamine	Same	3 mg./ 200 ml. NSS	Active vasodilator of minute vessels	Moderate increase in total flow (short duration); skin temperature rise in blush areas only	Substernal oppression, shortness of breath, burning of skin
Dibenzazepine phosphate	Ilidar	50 mg.	Adrenergic blocker	Marked increase in blood flow to skin with small increment to muscle	Dryness of throat, stuffiness of nose, tachycardia, occasional orthostatic hypotension, drowsiness, diarrhea
Nicotinic acid	Niacin	100 mg.	Vasodilator of minute blood vessels	Short-lived increase in total flow; skin temperature rise in blush areas only	Flushing of face and body, feeling of warmth, dizziness
Papaverine hydrochloride	Same	32 mg.	Antispasmodic	Increase in total flow; skin temperature rise in blush areas only	Shortness of breath, occasional chest pain, coughing paroxysm, sleepiness
Tolazoline hydrochloride	Priscoline	50 mg.	Partial sympatholytic agent	Increase in skin flow; occasional decrease, little or no increase in muscle flow	Burning of skin, tachycardia arrhythmias, abdominal pain, nausea, vomiting
Methionide of triaryl phosphoric ester	27 MI	50 mg.	Unknown	Occasional small increase in total flow	Dizziness, blurring of vision

intravenous and intra-arterial drug administration under controlled conditions, in both healthy subjects and in patients with documented occlusive arterial disease.

METHODS AND MATERIAL

Nine vasodilator agents were tested (Table 1). Immediate responses in extremity blood flow, surface temperature, blood pressure, and pulse rate were recorded in a control group of 17 subjects without evidence of cardiovascular or renal disease (average age 55, range 35 to 68) and in a group of 11 patients with documented obliterative disease of the peripheral arteries

(average age 65, range 51 to 76). The results of intravenous administration were compared with those achieved by intra-arterial injections in the two groups. In the group with obliterative disease the injection was made into the artery supplying the affected limb.

The procedure consisted of measuring blood flow to an extremity with a large-limb venous occlusion plethysmograph [18] in a constant temperature room under basal conditions. Evaluations of various forms of venous occlusion plethysmography as a measurement of rate of peripheral blood flow have been presented in the literature repeatedly.[7, 15] Adaptation to the environment (kept at 20° C. and 55% humidity) was ascertained by automatic quasi-continuous recording of surface temperature with a six-channel Speedomax. Since surface temperature recordings provide only an indication of blood flow to the skin bed, while this study deals with total blood flow to the extremity, a detailed report on surface temperature findings has been omitted. The surface temperature recordings also provided a comparison of blush and glomus areas.* [19] Estimation of cardiac output by means of sodium [20] dilution curves, and calculation of renal plasma flow from constant infusion of para-aminohippuric acid, was done in at least one experiment with each of the drugs in the control group. In the diseased group, these two latter observations were not made for technical reasons; however, this was not considered a serious drawback, since the results in peripheral blood flow were, directionally, very similar in the two groups. A total of 155 experiments was performed, each drug having been given about 15 trials.

Results

Control Group: The effects of the nine vasodilator drugs upon peripheral blood flow, surface temperature, cardiac output, and renal plasma flow given intravenously have been compared with those following intra-arterial injection (Table 2).

Total blood flow to the lower extremities increased in response to all agents, both on intra-arterial and intravenous administration. There were, however, marked quantitative variations. In all agents except chlorison amine and papaverine the increment in blood flow was always larger when the agent was given intra-arterially. Surface temperature recorded from a glomus area increased with the use of all nine agents; in seven, the increase was more marked on intra-arterial than on intravenous administration. Uniformly, responses occurred more promptly on intra-arterial administration. This was particularly marked with the use of nicotinic acid, papaverine, tolazoline hydrochloride, and methionide of triaryl phosphoric ester. Duration of responses varied with different drugs. The longest responses were recorded after ganglionic chlorison amine and adrenergic dibenzazepine phosphate blocking agents, and after the epinephrine-like substance

* Blush areas are chiefly face, neck, and upper anterior chest. The glomus areas are chiefly on fingers and toes.

TABLE 2

Effects of Vasoactive Agents in Healthy Subjects

Name of Agent	Mode of Administration	Average Increase in Blood Flow in %	Average Increase in Surface Temperature (C°)	Time (min.)		Average Change in			
				Maximal Response	Duration	Arterial Pressure (mm. Hg)	Pulse (rate/min.)	Cardiac Output	Renal Plasma Flow (PAH)
Arlidin	IV	61	No change	35	80				
	IA	82	+7.5°	30	65	±15/10	+15	+41%	+21%
Diethylamino ethanol	IV	60	+4.5°	41	47				
Ecolid	IA	74	+3.0°	23	35	−10/0	No change	−20%	+ 9.8%
	IV	73	+3.7°	44	90				
Histamine	IA	77	+5.0°	40	75	−30/29	+10	+43%	−12.9%
	IV	21	+4.0°	28	68				
Ilidar	IA	48	+5.5°	20	45	−25/15	+15	No change	−24%
	IV	41	+5.3°	57	80				
Nicotinic acid	IA	84	+8.0°	35	75	−20/10	+20	No change	+29%
	IV	51	+3.5°	20	50				
Papaverine	IA	98	+5.0°	15	40	−10/0	+10	+43%	+35.6%
	IV	47	+4.0°	59	70				
Priscoline	IA	49	No change	25	30	−15/10	No change	+42%	+17%
	IV	23	+5.5°	22	57				
27 MI	IA	33	+6.2°	5	25	−10/0	No change	No change	+35%
	IV	15	No change	40	65				
	IA	36	+3.1°	11	33	−10/0	+15	−52%	+20%

nylidrin hydrochloride (80 to 90 min.). Uniformly, duration of response was longer after intravenous than after intra-arterial administration; this was particularly striking with papaverine, tolazoline hydrochloride, and methionide of triaryl phosphoric ester.

Cardiac output increased after administration of nylidrin hydrochloride, chlorison amine, nicotinic acid, and papaverine hydrochloride. It decreased with the use of diethylamino ethanol and methionide of triaryl phosphoric

TABLE 3

Effects of Vasoactive Agents in Patients with Occlusive Arterial Disease

Name of Agent	Mode of Administration	Average Increase in Blood Flow in %	Average Change in Surface Temperature (C.)	Time (min.)		Average Change in	
				Maximal Response	Duration	Arterial Pressure (mm. Hg)	Pulse (rate/min.)
Arlidin	IV	72	−0.7°	45	57		
	IA	117	−1.3°	29	50	±15/15	+15
Diethylamino ethanol	IV	93	+3.5°	41	55		
Ecolid	IA	92	+3.0°	20	60	−20/10	+10
	IV	130	+3.0°	65	125		
Histamine	IA	90	+0.5°	35	95	−30/20	+10
	IV	67	+3.0°	52	100		
Ilidar	IA	145	+7.5°	46	95	−25/15	+20
	IV	76	+8.0°	78	74		
Nicotinic acid	IA	125	+6.5°	68	125	−15/10	+10
	IV	150	+1.0°	29	69		
Papaverine	IA	125	No change	10	70	±15/10	+10
	IV	87	+2°	50	65		
Priscoline	IA	215	No change	15	40	±15/10	No change
	IV	16	+5.5°	42	50		
27 MI	IA	93	+4.0°	24	37	±15/10	±15
	IV	39	+2.5°	52	30		
	IA	76	+3.5°	25	46	−15/10	+15

ester. It remained unchanged with histamine, dibenzazepine phosphate, and tolazoline hydrochloride. Renal plasma flow increased to some degree after all agents, except chlorison amine and histamine, after both of which there was a decrease in renal plasma flow. A striking increase in renal plasma flow was recorded after nicotinic acid. The responses in cardiac output and renal plasma flow were comparable after intravenous and intra-arterial administration.

There was a significant drop in systemic arterial pressure only after the use of chlorison amine and histamine; the other seven agents affected arterial pressure very little, regardless of route of administration.

Patients with Documented, Nongangrenous, Occlusive Arterial Disease: As in the control group, total blood flow increased in response to all of the nine agents (Table 3). The percentile increases were greater than those found in the control group, because of the lower resting flow (2 to 8 ml./min. per 100 ml. of tissue, as compared with 8 to 25 ml. in the control group). In response to six of the nine agents, namely, nylidrin hydrochloride, histamine, dibenzazepine phosphate, papaverine, tolazoline hydrochloride, and methionide of triaryl phosphoric ester, the increase in blood flow was greater after intra-arterial administration than after intravenous administration; chlorison amine (ganglionic blocker) and nicotinic acid showed the reverse. There was no difference when diethylamino ethanol was used.

The surface temperature rose considerably after administration of dibenzazepine phosphate, histamine, and tolazoline hydrochloride, but showed no appreciable change after that of nylidrin hydrochloride. Nicotinic acid and papaverine produced minor changes in surface temperature, recorded at the glomus areas. Intra-arterial administration produced a more prompt response than intravenous administration, as is shown in the control group.

There was a delay in reaching maximal increase in blood flow with some of the drugs in the group with obliterative arteriosclerosis, compared with the control group. This delay occurred with seven drugs (all except diethylamino ethanol and papaverine) following intravenous administration, and with four agents (histamine, dibenzazepine phosphate, tolazoline hydrochloride, and methionide of triaryl phosphoric ester) following intra-arterial administration. Duration of blood flow responses in the arteriosclerotic group was longer than in the control group with all agents except nylidrin hydrochloride on intra-arterial administration and papaverine, tolazoline hydrochloride, and methionide of triaryl phosphoric ester on intravenous administration. As in the control group, only chlorison amine and histamine produced significant lowering of arterial pressure, while blood pressure changes were minimal following the use of other agents.

Discussion

Responses were noted earlier when the agent was administered intra-arterially, but lasted longer when the intravenous route was used. This

was true for both the patients with obliterative arterial disease and for the control group. Therefore, when an immediate response is desired, the intra-arterial route is superior; otherwise intravenous administration may be more useful. Responses in blood flow were also of greater magnitude after intra-arterial administration than after intravenous administration, which finding fortifies the conclusion that the intra-arterial route is more desirable whenever immediate increase in regional blood flow is needed.

In this study, surface temperature was useful only in indicating the distribution of the increment in blood flow within the limb, i.e., greater or lesser degree of participation of the skin bed as a result of induced vasodilation.[20] Nylidrin, a substance related to Adrenalin, which is known to produce primarily an increase in blood flow to muscle, did not increase surface temperature. Dibenzazepine, a substance related to Dibenamine, which is known to produce primarily an increase in skin flow, caused marked increase in surface temperature. This is noteworthy since these differences in responses occurred in the presence of comparable increases in total blood flow to the limb. These single dose studies again point to the necessity of considering carefully the site of action of each peripheral vasodilator.

With most of the agents used (including diethylamino ethanol) increase in peripheral blood flow was not associated with major changes in arterial pressure. Administration of a ganglionic blocker and of histamine to a lesser degree were, however, associated with a considerable drop in systemic arterial pressure. With a majority of agents producing increase in blood flow to an extremity, the effect seems unrelated to generalized vasodilation.

The two agents (the ganglionic blocker and histamine) which lowered systemic arterial pressure to any great extent were the only ones to be followed by a decrease in renal plasma flow. Because of their hypotensive effect ganglionic blockers and, to a lesser degree, histamine are presumably not to be generally recommended as agents for production of increase in local peripheral blood flow. Moreover, their effect on renal plasma flow militates against their use where maintenance of renal blood flow is important.

Side Effects: The only drug which caused serious side effects was the ganglionic blocker, which induced severe hypotension (Table 1). The use of adrenergic blockers and of Adrenalin-like substances calls for caution in patients with associated heart disease, particularly those with coronary artery disease. Adrenergic blockers may also become troublesome in patients with chronic pulmonary disease and a tendency to bronchospasm. In this study, no essential differences were observed in side effects in a comparison of the intra-arterial with the intravenous route of administration. Undesirable effects were, however, more frequent and pronounced in the diseased group than in the controls. The effects on blood flow were of greater magnitude percentagewise in the patients with vascular disease than in the control group, and the onset of vascular responses was delayed.

Summary

Nine agents were tested for their actions on peripheral blood flow. In 155 single dose experiments in man, intra-arterial and intravenous administration were compared in 17 controls and in 11 patients with nongangrenous obliterative arteriosclerosis of the lower extremities.

Blood flow to the leg and foot and renal plasma flow were measured. Cardiac output was estimated. Arterial pressure, pulse rate, and surface temperature were recorded. Onset, duration, and magnitude of responses were charted.

The intra-arterial route may be superior to the intravenous route in an acute emergency, in that a faster and greater increase in blood flow occurred, but the intravenous route gave a more prolonged response. Most agents capable of increasing blood flow to the extremities are without effect on systemic arterial pressure. Side effects are independent of the route of administration.

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Summario in Interlingua

Esseva studiate le responsas vascular al administration intra-arterial e intravenose de agentes chimic sub conditiones controlate, tanto in subjectos normal como etiam in patientes con documentate morbo arterial.

Novem agentes de vasodilatation esseva testate. Le responsas immediate in fluxo de sanguine in le extremitates, in temperatura superficial, in tension de sanguine, e in le frequentia del pulso esseva registrate in un gruppo de controlo de 17 subjectos libere de omne indicio de morbo cardiovascular o renal (de etates de inter 35 e 68 annos, con un etate medie de 55 annos) e in un gruppo de 11 patientes con documentate morbo oblitterative del arterias peripheric (de etates de inter 51 e 76 annos, con un etate medie de 65 annos).

In le gruppo de controlo, le fluxo de sanguine total verso le extremitates inferior cresceva a varie grados in responsa a omne le agentes testate tanto per via intra-arterial como etiam per via intravenose. In le casos de omne le agentes, con le exception de chlorisonamina e papaverina, le augmento del fluxo de sanguine esseva semper plus marcate e plus prompte quando le agente esseva administrate per via intra-arterial. Le temperatura superficial in le area de un glomo montava post le uso de omne le novem agentes.

Le rendimento cardiac cresceva post administrationes de cinque del drogas. Le fluxo de plasma renal se intensificava plus o minus marcatemente post omne le agentes con le exception de chlorisonamina e histamina. Le augmento esseva frappante post acido nicotinic. Le responsas in rendimento cardiac e fluxo de plasma renal esseva comparabile post administrationes intravenose e post administrationes intra-arterial.

Un reduction significative del tension systemico-arterial esseva constatate solmente post chlorisonamina e histamina.

In le gruppo de patientes con arteriosclerosis oblitterative, le fluxo de sanguine total esseva etiam augmentate in responsa a omne le novem agentes. Le procentages del augmentos esseva plus grande que in le gruppo de controlo (a causa del plus basse valores de base), sed un retardo in le attingimento del maximos de fluxo de sanguine

esseva notate in comparation con le gruppo de controlo. Solmente chlorisonamina e histamina produceva significative reductiones del tension arterial.

Le effectos lateral non depende del via de administration.

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TUBERCULOUS PERITONITIS *

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IF advances in specific therapy and refinements in diagnostic procedures are to be fully utilized, the clinical patterns of infection require periodic critical re-evaluation and perhaps modification. Although tuberculous peritonitis was well described in the early 1900s,[1-12] except for several recent reports [13-16] it has received little attention in English medical literature subsequent to the widespread utilization of cultural methods for the identification of tubercle bacilli, the employment of tuberculin skin tests, and the introduction of effective specific chemotherapy.

This discussion reviews the clinical spectrum of tuberculous peritonitis and emphasizes the clinical features of the "ascitic" type of tuberculous peritonitis (a form not emphasized in recent reports), which often presents as an illness of abrupt onset, with fever and rigors, without associated leukocytosis, and in which negative tuberculin skin tests may be found in patients who are not overwhelmingly ill.

CLINICAL MATERIAL

All records, clinical and autopsy, of the Parkland Memorial Hospital were reviewed in which the diagnosis of tuberculous peritonitis was made between the years of 1943 and 1960. Records were excluded which contained insufficient information to establish a diagnosis or concerned patients in whom tuberculous peritonitis represented an incidental aspect of miliary or far advanced terminal tuberculosis. Thus, tuberculosis of the peritoneum represents the major site of tuberculous involvement in the patients being reported.

A diagnosis of tuberculous peritonitis was accepted only if (1) acid-fast bacilli morphologically typical of *Mycobacterium tuberculosis* were demonstrated on smear of ascitic fluid in association with peritoneal "tubercles," (2) *Myco. tuberculosis* was cultured from ascitic fluid, or (3) acid-fast bacilli were demonstrated in caseous granulomas on microscopic section of peritoneal tubercles.

Twelve patients who met these criteria form the basis of this report. Four of these patients were seen by the authors.

CLINICAL OBSERVATIONS

The salient clinical features observed in this series of patients are recorded in Table 1. There is a predominance of women: eight females to

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four males. The average age of the male patients was 55 years; in the group of females, the average age was 35 years. There was also a greater frequency of occurrence in the Negro race (11 of 12 patients).

A history either could not be obtained or was unreliable in three patients. Seven of the remaining nine complained primarily of increasing abdominal girth, which often was of short duration, being of less than two weeks' duration in four patients. In two patients, abdominal pain was the most prominent complaint and in both it was of short duration. The history of frank shaking chills with fever was elicited from four of the seven patients queried.

TABLE 1

Clinical Features of Tuberculous Peritonitis

Case No.	Race* Sex	Age	Basis of Diagnosis*	Presenting Complaints		Temp. °F.	Rigors*	Major Physical Sign	Evidence of Cirrhosis
				Symptom	Duration				
1	NM	73	Cas. gran. Atpsy.	Moribund	N.R.	99.6	N.R.	Distended abdomen	No
2	WF	21	Cas. gran. Bpsy.	Abd. pain	7 days	98.8	N.R.	RLQ tenderness	No
3	NF	41	AFB—Bpsy.	Abd. enlargement	3 mo.	104.2	Yes	Ascites	No
4	NM	25	AFB—Cult.	Abd. enlargement	8 days	101.0	No	Ascites	No
5	NF	17	AFB—Smear	Abd. cramps and enlargement	8 days	102.8	Yes	Ascites	No
6	NF	30	Cas. gran. Bpsy.	Abd. pain	14 days	98.2	N.R.	Ascites	Yes†
7	NF	62	Cas. gran. Atpsy. AFB—Cult.	Moribund	N.R.	99.0	No	Rigid abdomen	No
8	NF	18	AFB—Cult. AFB—Bpsy.	Diarrhea, abd. enlargement	7 days 1 day	103.6	Yes	Ascites	No
9	NF	51	Cas. gran. Bpsy.	Abd. enlargement	2½ mo.	98.6	N.R.	Ascites	No
10	NF	42	AFB—Cult. Bpsy.	Abd. enlargement	17 days	103.6	Yes	Ascites	No
11	NM	66	Cas. gran. Atpsy.	Abd. enlargement	14 days	99.6	Yes	Ascites	Yes
12	NM	55	AFB—Bpsy.	Unreliable	—	99.8	N.R.	Abd. tenderness	No

* Legends: N, Negro (male, female); W, Caucasian; N.R., not recorded; AFB, acid-fast bacilli; Cas. gran., caseous granulomas; Atpsy., autopsy; Bpsy., biopsy; Cult., culture.
† History of alcoholism; liver function studies not performed.

Five of the 12 patients had temperatures of greater than 100° F. on admission. The most striking sign on physical examination was ascites, which was present in eight patients. In several patients the ascites was of marked degree and did not give the impression of being loculated. There were clinical findings to suggest cirrhosis in only two patients.

There was no evidence of tuberculous involvement of the fallopian tubes in six of the eight women in the series (Table 2). Previous hysterectomy and bilateral salpingo-oöphorectomy had been performed on two of the patients. Seven of the eight females had been pregnant and had delivered viable infants, and one patient (case 5) subsequently became pregnant. It is of note that one patient (case 5) delivered three months prior to admission and another patient (case 8) had a spontaneous abortion three and one-half

TABLE 2

Evidence of Pelvic Tuberculosis in Female Patients

Case No.	Age	Maternity Status*			Tubo-ovarian Abscess
		G.	P.	Ab.	
2	21	2	1	1	No
3	41	1	1	0	No—Hyst. and BSO 1 yr. PTA
5	17	1	1	0	No—Delivered 3 mo. PTA, subsequent pregnancy
6	30	1	1	0	Probable
7	62	2	2	0	No
8	18	2	1	1	Yes—About 3½ wks. PTA
9	51	0	0	0	No—Hyst. and BSO 13 yrs. PTA
10	42	2	2	0	No

* Legends: G., gravid; P., parity; Ab., abortion; Hyst., hysterectomy; BSO, bilateral salpingo-oöphorectomy; PTA, prior to admission.

weeks prior to admission. An apparent association between pregnancy and tuberculous peritonitis was suggested by Kelly; [2] however, this was not substantiated by the observations of Faulkner and Everett.[7]

Laboratory findings in this series of patients are recorded in Table 3. Anemia was present in all 10 patients in whom initial hemoglobin values

TABLE 3

Laboratory Features in Tuberculous Peritonitis*

Case No.	Inanition	Temp. (°F.)	Hgb. (gm. %)	Peripheral WBC (1,000/cu. mm.)	Differential Count		Tuberculin Test		Initial Chest X-ray
					PMN %	Lymphs. %	Prep.—Strength	Result	
1	No	99.6	6.5	8.5	79	13	N.D.		Neg.
2	No	98.8	13.0	8.0	65	22	N.D.		Bilat. apical infiltrate
3	Probable	104.2	9.0	14.0	76	18	PPD-2	+	Lt. pleural effusion
4	No	101.0	N.D.	N.D.	—	—	OT 1:1,000	+	Neg.†
5	No	102.8	8.0	5.0	52	30	OT 1:1,000	+	Bilat. basilar infiltrate
6	No	98.2	8.7	7.9	75	25	N.D.		Rt. pleural effusion
7	Yes	99.0	9.8	6.3	72	28	PPD-2	−	Blunt. lt. C-P angle
8	No	103.6	9.8	9.8	82	14	PPD-2	−	Rt. pleural effusion
9	No	98.6	9.0	4.3	60	38	OT 1:100	+	Blunt. lt. C-P angle
10	No	103.6	11.2	5.0	86	11	PPD-2	+	Blunt. lt. C-P angle
11	No	99.6	N.D.	6.3	86	14	OT 1:1,000	−	Lt. pleural effusion
12	Yes	99.8	8.8	4.5	76	22	PPD-2	−	Rt. pleural thickening

* Legends: OT, old tuberculin; PPD, purified protein derivative; N.D., not done; + positive; − negative; C-P, costophrenic.

† At one-year follow-up, had moderately advanced pulmonary tuberculosis.

TABLE 4

Liver Function Tests in Patients With Tuberculous Peritonitis

Case No.	Temp. (°F.)	Evidence of Cirrhosis	Bilirubin (mg. %)	Serum Albumin (gm. %)	Serum Globulin (gm. %)	Alkaline Phosphatase	Cephalin Cholesterol Floc.	BSP (%)
1	99.6	No	N.D.*	N.D.	N.D.	N.D.	N.D.	N.D.
2	98.8	No	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
3	104.2	No	0.2	3.4	4.0	5.4	3+	9
4	101.0	No	N.D.	3.6	4.2	N.D.	N.D.	0
5	102.8	No	N.D.	3.1	3.4	N.D.	1+	11
6	98.2	Yes†	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
7	99.0	No	0.7	2.9	1.5	4.1	1+	N.D.
8	103.6	No	1.6	2.5	2.1	2.3	0	10
9	98.6	No	0.3	4.0	4.8	2.2	0	12
10	103.6	No	0.2	3.2	3.2	2.5	2+	21
11	99.6	Yes	1.0	3.8	3.6	5.7	3+	17
12	99.8	No	0.7	2.2	3.0	3.6	3+	25

* N.D., not done.
† Definite history of alcoholism.

were recorded, and in eight patients hemoglobin concentrations were less than 10 gm.%. Initial leukocyte counts were less than 10,000 per cubic milliliter in 10 of the 11 patients. In eight of the 11 patients, the differential leukocyte counts showed greater than 70% neutrophils.

Tuberculin skin tests were performed on nine patients at admission (Table 3). It should be noted that three of the nine patients had negative tests utilizing second strength PPD (0.005 mg.) and one had a negative test utilizing 1:1,000 old tuberculin. Of the four patients with negative tuberculin reactions, only two might have been anticipated to demonstrate hypoergia to tuberculin: one was overwhelmingly ill (case 7) and the other was cachetic (case 12).

Initial x-ray films of the chest demonstrated infiltrative lesions in only two patients. Evidence of pleural effusion, pleural thickening, or blunting of the costophrenic angle was noted in eight patients. In two patients the chest films were within normal limits.

Liver function studies were performed in nine of the 12 patients (Table 4). Retention of bromsulfalein was noted in seven of the eight patients

TABLE 5

Ascitic Fluid

Case No.	Color/Character	Sp. Grav.	Protein (gm. %)	Result of AFB Smear/Culture	Sugar (mg. %)
3	—	1.024	—	Not done	—
4	—	1.022	7.2	Culture positive	69
5	—	1.022	5.0	Smear positive	75
8	Greenish	—	—	Culture positive	—
9	Yellow/turbid	1.026	6.3	Not done	—
10	Greenish-yellow	1.017	5.0	Culture negative	—
11	Straw	1.014	5.1	Culture negative	—
12	Serosanguinous	—	2.4	Culture negative	—

studied; however, four of these patients were febrile. Serum albumin levels were less than 3 gm.% in three of nine patients and in six patients the concentration of serum globulin was equal to or greater than the concentration of albumin. Although it is difficult to be certain of the presence of cirrhosis, only two of these patients were clinically considered to have cirrhosis.

Samples of ascitic fluid obtained from eight patients were studied (Table 5). The protein content was greater than 5 gm.% in five of the six fluids analyzed. The concentration of sugar was normal in the two instances in which it was determined. Cultures and/or smears were positive for *Myco. tuberculosis* in three of six fluids, including the two specimens with normal sugar concentrations.

TABLE 6

Course of Tuberculous Peritonitis

Case	Therapy	Follow-Up (years)	
		Results	Duration
1	—	Died	—
2	—	Lost	—
3	INH–PAS SM	OK	3
4	SM	Lost	1*
5	INH–PAS SM	OK	6
6	INH–PAS	OK	6
7	—	Died	—
8	INH–PAS	OK	1
9	INH	OK	4
10	INH–PAS	OK	9/12
11	—	Died	—
12	INH–PAS	OK	7/12

* At one-year follow-up had moderately advanced pulmonary tuberculosis.

The course of these patients is summarized in Table 6. Eight patients received antituberculous therapy of some type. The single patient treated with streptomycin alone (case 4) demonstrated improvement of the peritoneal disease; however, pulmonary tuberculosis developed during the course of therapy. Wichelhausen and Brown noted recovery in 23 of 26 patients treated with streptomycin alone; yet extraperitoneal tuberculosis was not controlled in eight of their patients.[18] The seven patients treated with isonicotinic acid hydrazide, either alone or in combination with streptomycin and/or para-aminosalicylic acid, have responded well.

DISCUSSION

The general clinical features of tuberculous peritonitis previously have been well documented. These features, which are exemplified by this group of patients, include more frequent occurrence in the 20- to 40-year age group, a predilection for females, and a disproportionately greater frequency of

occurrence in Negroes. A recent review of 34 patients seen at the Mayo Clinic between 1940 and 1958 differs from our experience; 19 of their patients were males, 20 patients were over 40 years of age, and the onset of symptoms was insidious in all but two patients.[16] These differences most likely result from patient selection; our patients are medically indigent and 66% of total admissions are Negroes.

A family history of tuberculosis was not elicited from any of our patients; however, there has been a family history of tuberculosis elicited from one-third of the patients in most of the older series.[3-5, 7]

Tuberculous peritonitis has been subdivided on the basis of broad clinical features into two major types: (1) the plastic or adhesive type, and (2) the exudative or serous type. The relative frequency of occurrence of either form varies considerably. Faulkner and Everett[7] noted 58% adhesive type and 22% serous type in 187 female patients, while Kahrs[14] reported 18% fibrotic, 44% serous, and 33% serofibrotic in a group of 169 patients (58% females).

Symptoms in the plastic, fibroid type tend to be chronic with abdominal pain being a more prominent complaint than abdominal swelling. Fever is usually of low grade, and Osler[1] commented on the occurrence of subnormal temperatures in occasional patients. Examination of the abdomen commonly reveals tenderness, occasional rigidity, or abdominal masses. The often described "doughy" abdomen is infrequently seen, being noted in 10% or less of patients.[4, 8, 11, 12, 15, 16] This is the form of tuberculous peritonitis stressed in current textbooks.[17-19]

The exudative or serous form occurred in nine of the 12 patients in this series in whom tuberculous peritonitis represented the major site of tuberculous involvement. The diagnosis of this form of tuberculous peritonitis often has been confused either with acute bacterial infections, particularly typhoid fever, or with intra-abdominal neoplasms.[1, 2] As observed in this group of patients, prominent symptoms included the relatively rapid onset of abdominal pain and swelling, which were often associated with fever and frank shaking chills. The occurrence of frank shaking chills has been noted by other authors;[2, 13, 15] however, this feature has not been stressed, and is often responsible for considerable delays in diagnosis, since rigors usually suggest bacterial infections rather than tuberculosis. The abdominal swelling is often associated with definite ascites. The specific gravity of the ascitic fluid exceeded 1.020 in three-fourths of patients in most reports,[3, 12] except that of Burack and Hollister.[15] Identification or isolation of *Myco. tuberculosis* by culture of ascitic fluid has been infrequent.[2, 13, 15] Laboratory findings usually include anemia and a normal peripheral leukocyte count, the peripheral leukocyte counts being less than 10,000/cu. mm. in from 70 to 95% of patients.[3, 5, 8, 13, 15, 16]

X-ray films of the chest are usually normal, or may reveal pleural fluid or nonspecific changes such as pleural thickening. The absence of infil-

trative lesions suggestive of tuberculosis as noted by us in these patients has been reported in other series.[15, 16]

A most striking clinical feature, which often delays a correct diagnosis and which was first mentioned, though not emphasized, in the recent paper by Hughes et al.[16] is the frequency of negative skin reactions either to purified protein derivative or to "old tuberculin" in patients who are not debilitated. Of the papers published in English which were reviewed, Shattuck recorded three negative reactions in 13 patients tested;[3] however, at that time interpretation was based upon a febrile response as a "positive" test. Burack and Hollister record the results of only one test, which was positive.[15] Hughes and co-investigators[16] noted negative skin reactions to both first and second strength PPD in three of 18 patients (17%). These three patients were not considered to be overwhelmingly ill.

TABLE 7

Sequence of Tuberculin Reversion in Case 8

Date	Tuberculin Test		Comment
	Strength	Result	
5/4/58	PPD-2	Neg.	Rt. pleural effusion
7/7/58	OT 1:1,000	Neg.	Admitted—ascites
7/9/58	OT 1:100	Neg.	
7/14/58	OT 1:1,000	Neg.	
8/8/58	PPD-1	Pos.	
8/19/58	OT 1:1,000	Pos.	

It has been stated that, except in extremely debilitated patients, negative skin reactions virtually exclude tuberculosis as an etiologic agent.[20] This is particularly true in patients with serous tuberculous pleural effusions.[21] However, there are several reports in the foreign literature which point out that tuberculous peritonitis may be present without a positive skin test.[22, 23]

The sequence of events noted in one young healthy patient (case 8) in this group suggests a mechanism for this seemingly paradoxical observation. This patient rapidly developed ascites in association with fever and rigors. At the time of admission, one day later, she had ascites and negative skin tests to both first and second strength PPD (0.005 mg., Table 7). A presumptive diagnosis of tuberculous peritonitis was made, and antituberculous therapy was instituted. The diagnosis was subsequently confirmed. Four weeks after admission, repeat skin tests were positive. Similar reversion of negative results to tuberculin tests employing second strength PPD to positive results after initiation of therapy was observed by Lester and Atwell; however, all of their patients had overwhelming illnesses.[24] Dworski et al.[25] demonstrated that injection of small numbers of tubercle bacilli into the peritoneal cavities of tuberculin-positive guinea pigs resulted in the outpouring of a volume of fluid several times greater than that observed following the same procedure in a normal tuberculin-negative animal. Oliviera-

Lima [26] has shown that it is possible to hyposensitize tuberculin-positive individuals to as much as 10 mg. of old tuberculin by the repetitive administration of defatted BCG organisms and old tuberculin. It seems reasonable to postulate the following sequence: A tuberculin-positive patient inoculates his peritoneal cavity with tubercle bacilli and/or their products, which results in the rapid development of ascites and a constitutional tuberculin reaction, including fever and rigors. Conceivably, the quantity of "tuberculin" or tubercle bacilli absorbed is sufficient to hyposensitize the patient for a period of weeks; following this period, tuberculin skin test sensitivity reappears.

The occurrence of tuberculous infections of the peritoneum in patients with cirrhosis and ascites noted by Osler [1] and Rolleston,[6] and recently reemphasized by Burack and Hollister,[15] often results in failure to suspect the tuberculous process. While this association occurred infrequently in our series of patients, the excellent studies of Burack and Hollister demonstrate the necessity for re-evaluation of patterns of infection.

Thus, tuberculous peritonitis may present as a syndrome characterized by the acute development of ascites in an individual who is apparently tuberculin-negative. It may also present as the well-described syndrome of ascites in tuberculin-positive individuals; the syndrome of unexplained fever both in cirrhotic and in older patients; the syndrome of chronic plastic fibroid peritonitis; or the syndrome of a fibrous encysted abdominal tumor.

Summary

The clinical features of 12 patients with tuberculous peritonitis as the major site of tuberculous involvement have been reviewed. Three patients presented as the chronic fibroid form, whereas nine patients presented as the serous form. The serous form often began as an illness of abrupt onset manifested by abdominal swelling and fever, and without associated leukocytosis. This form of serosal tuberculosis often was associated with negative tuberculin skin tests. It is postulated that the mechanism for this clinical paradox involves the transient hyposensitization of a tuberculin-sensitive individual.

Summario in Interlingua

Es presentate un revista del characteristicas clinic de 12 patientes in qui peritonitis esseva le centro principal del affection tuberculotic. Iste characteristicas general include (1) un plus alte incidentia in le gruppo de etates de inter 20 e 40 annos, (2) un predilection pro femininas, e (3) un disproportionalmente frequente occurrentia in negros. Un anamnese familial de tuberculose non esseva documentate in ulle del casos de iste patientes. In tres le morbo se accusava in le forma fibroide chronic, in le altere novem in le forma serose. Le forma serose comenciava frequentemente abruptemente, manifeste per tumescentia abdominal e febre, e sin leucocytosis associate. Iste forma de tuberculose serosal esseva associate con negative tests cutanee a tuberculina in quatro del novem patientes. Es exprimite le opinion que le mechanismo del occurrentia de negative tests cutanee in patientes qui non es rabide-

mente malade depende de un hyposensibilisation transiente in un individuo qui es sensibile a tuberculina.

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ELECTROPHORETIC AND ANALYTICAL ULTRACENTRIFUGE STUDIES IN SERA OF PSYCHOTIC PATIENTS: ELEVATION OF GAMMA GLOBULINS AND MACROGLOBULINS, AND SPLITTING OF ALPHA$_2$ GLOBULINS * †

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Psychotic patients have been shown to have an excessive incidence of rheumatoid factor and lupus factor in their sera.[1, 2] This paper reports the electrophoretic serum protein patterns of chronically psychotic patients who had positive serologic tests for rheumatoid factor and the patterns of certain control groups.

Materials and Methods

A. *Patient Material:* The following sera of chronically psychotic patients were examined: (1) eighty-four sera known to contain rheumatoid factor (FII-positive group); (2) forty-six sera known not to contain rheumatoid factor or lupus factor (FII-negative group); (3) twenty-six sera, none of them containing the rheumatoid factor, obtained from a group of schizophrenic patients who had had the disease for from two to five years and who had definitely not received ataractic drugs during the past two years ("no drugs" group); (4) ten sera from male chronic schizophrenics who had had catatonic withdrawal to the point of mutism for from three months to two years in duration ("catatonic" group).

The psychiatric diagnoses and medical status (where relevant) of the patients in the FII-positive and FII-negative groups have already been published.[1]

B. *Controls:* An attempt was made to rule out long institutionalization as a factor by using as controls the sera from 50 long-term prisoners in Alcatraz Federal Penitentiary. None of these sera was found to contain rheumatoid factor or lupus factor.

C. *Analytical Methods:*

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TABLE 1

Quantitative Disturbances in Serum Proteins

Protein Fractions	FII-Positive (Total: 83)			FII-Negative (Total: 43)			No Drugs (Total: 26)			Catatonics (Total: 10)			Prisoners (Total: 50)		
	% Total Serum Protein		Number Showing Component	% Total Serum Protein		Number Showing Component	% Total Serum Protein		Number Showing Component	% Total Serum Protein		Number Showing Component	% Total Serum Protein		Number Showing Component
	Mean	S.D.		Mean	S.D.		Mean	S.D.		Mean	S.D.		Mean	S.D.	
Albumin	49.1	±7.7	83	51.7	±7.1	43	47.8*	±4.5	26	49.3	±6.2	10	50.8	±4.8	50
Post-albumin	3.0	±0.7	56	3.6	±0.9	34	4.1	±1.4	13	3.7	±0.1	8	5.0	+1.3	40
$Alpha_1$	5.7†	±1.7	83	5.6†	1.5	43	5.2†	±2.0	26	5.3	±1.6	10	6.7	±2.3	50
$Alpha_2$	13.4†	±2.5	83	13.2‡	±1.0	43	13.5	±2.6	26	11.7†	±2.0	10	14.9	±2.9	50
Total beta	9.2	±2.7	83	9.8	±2.3	43	11.6†	±2.0	26	12.2†	±2.8	10	9.6	±2.6	50
$Beta_1$	7.5	±1.6	19	8.2	±1.4	11	8.2	±1.4	20	8.6	±2.3	7	8.7	±1.7	21
$Beta_2$	3.9	±2.4	19	3.7	±1.1	11	3.6	±0.9	20	4.1	±1.3	7	2.9	±0.8	21
Gamma	21.2‡	±5.1	83	19.3*	±5.3	43	19.9†	±3.6	26	20.2*	±3.3	10	17.0	±3.9	50

Each group was compared with prisoners' sera using t-test for significant differences between albumin, $alpha_1$, $alpha_2$, total beta, and gamma globulin. FII-positive and FII-negative refer to sera of psychotic patients which did or did not contain rheumatoid factor. See text for explanation of "No drugs" and "Catatonics" groupings.

* Significant at 0.05 level.
† Significant at 0.01 level.
‡ Significant at 0.001 level.

1. Serum electrophoresis and quantification were carried out in a microelectrophoresis cell using cellulose acetate as the supporting medium.[3] Approximately 0.25 μL. of serum were applied to cellulose acetate strips 1.3 cm. wide by 13.5 cm. long; a voltage of approximately 15 per cm. was applied for two hours, using a veronal buffer, pH 8.6, ionic strength 0.075. The strips were stained for protein with Ponceau-S. Quantification of the protein separation was then obtained by a Spinco Analytrol fitted with a modified microanalyzer attachment.[3]

2. Analytical ultracentrifugation of certain sera was performed by the Institute of Medical Physics, Belmont, California.

3. All sera were stored at between — 15° and — 20° C. until they were required for analysis.

TABLE 2

Incidence of Qualitative Abnormalities in Serum Proteins

	FII-Positive (Total: 83)	FII-Negative (Total: 43)	No Drugs (Total: 26)	Catatonics (Total: 10)	Prisoners (Total: 50)
Split $alpha_2$ globulin	9* (11%)	1 (2%)	6† (23%)	0	0
Split beta globulin	19* (23%)	11 (26%)	20† (77%)	7 (70%)	21 (42%)
Line in gamma globulin	18 (22%)	8 (19%)	1 (4%)	1 (10%)	0
Abnormal shape of curve of gamma globulin	28‡ (33%)	14‡ (33%)	9‡ (35%)	1 (10%)	0

FII+, FII−, "No drugs," and "Catatonics," see footnotes to Table 1.

Figures were tested for significance (chi-square test) as compared to results in prisoners' sera. In those cases where the application of the chi-square distribution was questionable due to the small relative frequency, i.e., less than 10%, Poisson's distribution was utilized and, in all cases, indicated significance with $p \leq .0025$.

* Significant at 0.05 level.

† Significant at 0.01 level.

‡ Significant at 0.001 level.

RESULTS

The results in the five groups of sera are compared in Tables 1, 2, and 3. Figures 2 to 6 demonstrate some of the quantitative and qualitative changes which were found.

Quantitative Disturbances (Table 1): The sera from psychotic patients, in comparison to sera from long-term prisoners, showed a significant diminution in the mean $alpha_1$ and $alpha_2$ globulins. The mean total beta globulin tended to be elevated in certain groups. The mean gamma globulin was increased in all groups.

Qualitative Disturbances (Tables 2 and 3): As Table 2 shows, several qualitative disturbances were noted in many of the sera of the psychotic patients. These were: (1) The appearance of a distinct line superimposed upon the gamma globulin; (2) An abnormal shape of the gamma globulin curve, as obtained from densitometric analysis, consisting of a marked lateral skew, an unusually sharp peak, or both; (3) A splitting of the $alpha_2$ globulin; and (4) The more frequent presence of $beta_2$ globulin in the sera

TABLE 3

Ultracentrifugal Analyses of Serum Proteins

Serum Pt., Sex, Age	Group	Line in Gamma Globulin	Split Alpha$_2$	S19 Globulin (mg. per 100 ml. serum)	S11 Globulin (mg. per 100 ml. serum)	Psychiatric Diagnosis	Significant Physical Findings
A. R. (M 50)	FII+	+		208(0)		S.R. hebe.	
C. H. (M 65)	FII+	+		354(3)		C.B.S. (senile)	Left ventricular hypertrophy
C. L. (M 50)	FII+	+	+	242(1)		S.R. cat.	Hypertensive heart disease
B. O. (M 65)	FII+	+				S.R. par.	Rheumatic heart disease
C. R. E. (M 62)	FII+	+		283(3)		Presenile dementia	
C. R. I. (F 53)	FII+	+	+	511(6)		C.B.S. with epilepsy	Congenital skeletal deformities
De S. (F 62)	FII+	+		275(1)		Depressive psychosis	
H. I. (F 60)	FII+	+		345(2)		S.R. hebe.	Ehlers-Danlos syndrome
J. I. (F 73)	FII+	+		574(7)	467	C.B.S. (senile)	
L. A. (F 64)	FII+	+	+	332(2)		S.R. par.	Rheumatoid arthritis
L. O. (F 55)	FII+	+		413(4)	396	S.R. schizo., affective	Rheumatoid arthritis
L. U. (M 62)	FII+	+		484(5)	254	C.B.S. ?cause	Morning stiffness of knees
M. A. (M 54)	FII+	+		349(3)		S.R. cat.	Old myocardial infarction
M. A. R. (M 54)	FII+	+		550(3)		S.R. par.	
N. E. (M 30)	FII+	+		367(3)		S.R. cat.	Tietze's syndrome Club feet
V. I. (M 46)	FII+	+	+	321(2)		Psychosis with convulsions	Rheumatoid arthritis
Y. A. (M 31)	FII+	+	+	218(0)		S.R. par.	Dystrophic calcification
A. C. (M 17)	FII−	+				S.R.C.U.	
A. P. (M 30)	FII−	+		425(5)		S.R. cat.	Congenital skeletal deformities
B. R. (M 50)	FII−	+		184(0)		S.R. hebe.	
F. A. (M 68)	FII−	+				S.R. par.	Rheumatic heart disease
L. A. (M 50)	FII−	+		415(4)		S.R. hebe.	Micrognathism
M. E. (M 59)	FII−	+		403(4)	325	Korsakoff's psychosis	
N. E. (M 22)	FII−	+				S.R.C.U.	
V. I. (M 51)	FII−	+		311(2)		S.R. hebe.	
W. A. (M 52)	N.D.	+		206(0)			
L. O. (M 21)	Cat.	+		195(0)		S.R. cat.	
G. A. (F 38)	Out-patient	+	+	533(4)		S.R.C.U.	

S19 = amounts of S19 macroglobulin expressed as mg./100 ml. serum.

S11 = refers to amount of protein, in mg./100 ml. serum, sedimenting out with a sedimentation constant in the ultracentrifuge of S11. This is never found in health; the prototype of this protein is found in multiple myeloma.

Figures in parentheses refer to the number of standard deviations from the mean for the patient's age and sex by which the value is elevated.

FII+, FII−, and "No drugs," see footnotes to Table 1.

S.R. = schizophrenic reaction.

Hebe. = hebephrenic.

Cat. = catatonic.

C.U. = chronic undifferentiated.

Par. = paranoid.

C.B.S. = chronic brain syndrome.

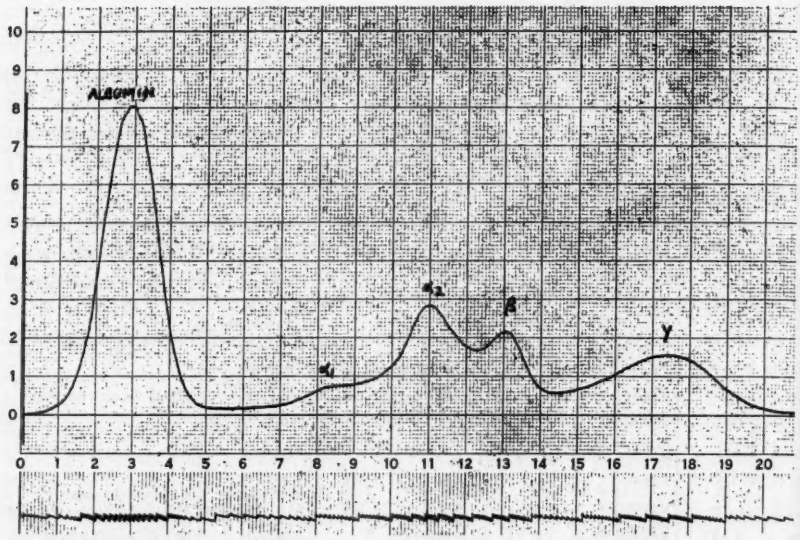


FIG. 1. Control serum obtained from prisoner. Normally shaped gamma curve.

of psychotics than in controls. Examples of these disturbances are shown in Figures 2 to 6. It is emphasized that no disturbance, other than the presence of beta$_2$ globulin, was seen in any of the 50 control sera; that disturbances were found in the group known not to have received drugs for at

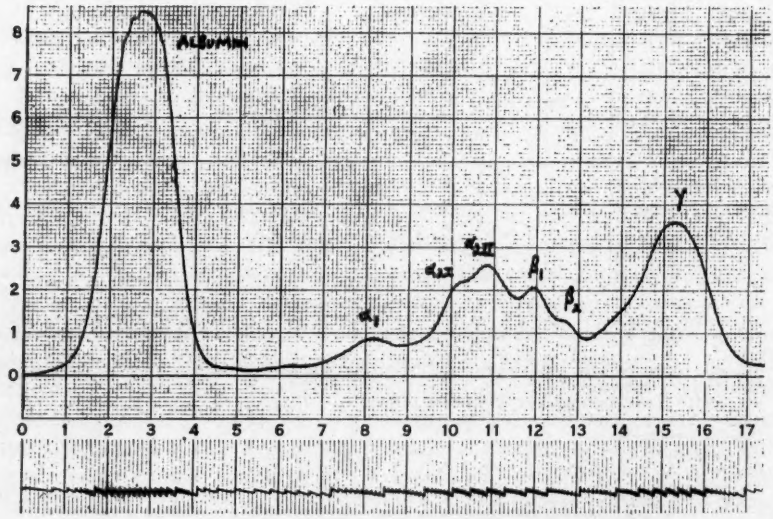


FIG. 2. Serum of patient with depression. Distinctly split alpha$_2$.

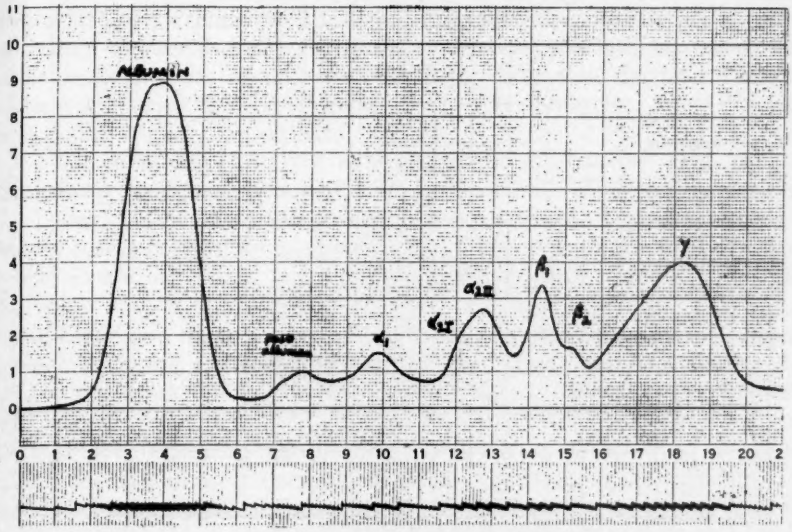


FIG. 3. Serum of patient with psychotic depression. Eight distinct fractions present, including split alpha$_2$ and prominent beta$_2$.

least two years; and that the serum taken from an outpatient schizophrenic, who had not been in a state hospital for over two years, showed both the splitting of the alpha$_2$ globulin and the band formation within the gamma globulin.

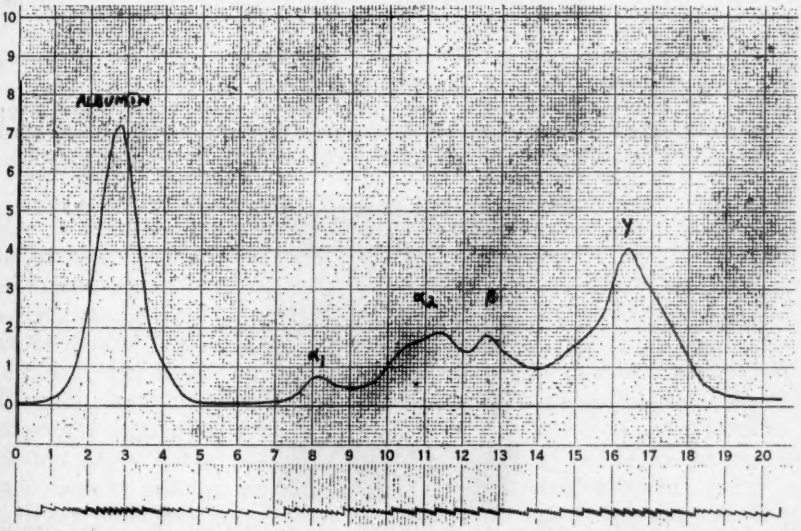


FIG. 4. Serum of patient C.R.I. (see Table 3). Distinctly split alpha$_2$. Sharp peak in gamma, which gives an abnormally shaped curve.

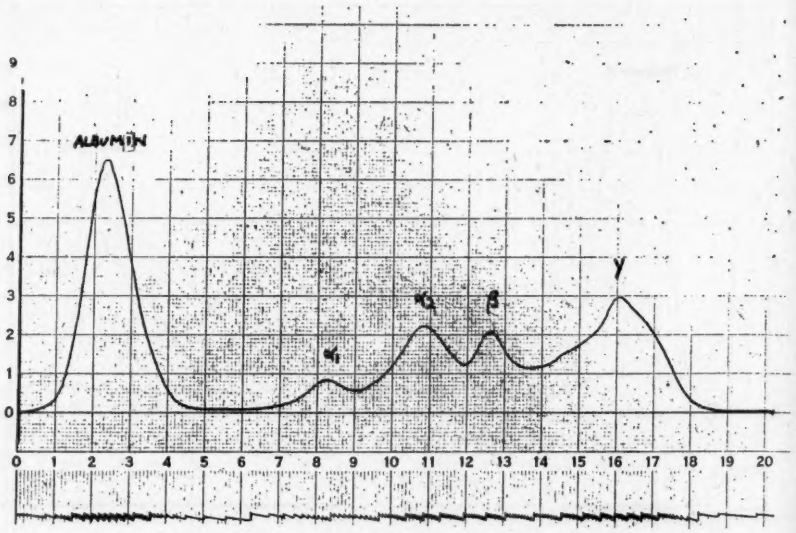


FIG. 5. Serum of patient C.R.E. (see Table 3). Abnormally shaped gamma curve.

Table 3 shows ultracentrifugal analyses of 24 sera (16 FII-positive and 8 FII-negative) in all of which the line in the gamma globulin was present and in some of which the splitting of the alpha$_2$ globulin was seen. Of these 24 sera, 17 (12 FII-positive and 5 FII-negative), showed an elevation of the S19 macroglobulin which was two standard deviations or more from the mean for the patients' age and sex.

DISCUSSION

This investigation was made because we had previously noted [1, 2] a higher incidence of rheumatoid factor and lupus factor, which are gamma globulins,

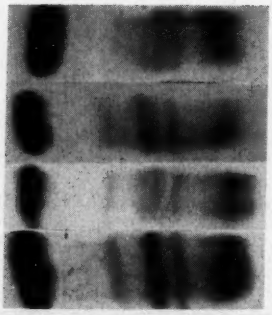


FIG. 6. Sera from four patients showing the line superimposed upon the gamma globulin band (at the right hand side of the strips).

in the sera of psychotic patients than in the sera of control subjects. Examination of those psychotic patients showed only a few to have rheumatoid arthritis despite the excessive incidence of rheumatoid factor. The incidence of systemic lupus erythematosus and other connective tissue diseases was slightly higher than expected.

There is evidence that the hypergammaglobulinemia we have demonstrated may result, at least in part, from an elevation in serum macroglobulin.

1. About 33% of sera of psychotic patients (Table 2) had abnormally shaped curves of the gamma globulin. Such curves must result from a disproportionate increase of one, or several, of the many components of this fraction.

2. Of 24 sera which showed a definite line superimposed upon the gamma globulin (on the electrophoresis strip) and which also had abnormally shaped gamma globulin curves (in the densitometric analysis), 17 contained S19 macroglobulin in amounts greater than two standard deviations from the mean for the patients' age and sex (Table 3).

3. The lines in the gamma globulin had a high dye uptake when stained for carbohydrate with periodic acid-Schiff (a high carbohydrate content is characteristic of macroglobulin [4]). Some hypergammaglobulinemic sera showed no lines in the gamma globulin when stained with Ponceau-S but showed clear lines when stained with periodic acid-Schiff. (These sera are not included in line 3 of Table 2.)

4. After one patient (G. A., Table 3) had been given penicillamine (which dissociates macroglobulins), 1 gm. orally per day for ten days, her serum no longer showed the line in the gamma globulin.

It seems probable that the elevation of macroglobulins found in some psychotic patients may account for the higher than normal incidence of positive FII tests we have reported.[1, 2] S19 globulin, other than that present in the serum of patients with rheumatoid arthritis, may occasionally have the property of combining with S7 globulin and of producing a positive FII test.

We are interested in the possibility that the hyperglobulinemia may play an important role in the pathogenesis of the psychosis. Two possibilities might be considered. First, it is known that many class S19 substances in human serum have antibody-like behavior.[4] Conceivably, a particular macroglobulin may have an affinity for specific constituents or essential metabolites of brain and, in excess, may cause brain damage or dysfunction at a molecular level. In support of this idea is the case of a patient with Waldenström's macroglobulinemia who had a hemiparesis and epilepsy; at autopsy no cerebral pathology was found to account for these symptoms.[5] Second, there is the likelihood that hypergammaglobulinemia reflects an auto-immune process, with the patient's own cerebral substance being an antigen. We have no evidence to support this idea. Only one serum of 310 sera from psychotic patients formed precipitins in a reaction with calf

brain extract.[2] Although about 10% of these sera gave inconstant and variable complement fixation reactions with a brain extract, normal sera behaved similarly.

In studying such abnormalities, it is most important to recognize that a host of coincidental factors may cause disturbances in the body fluids of psychotic patients. Malnutrition, the disturbance in physiology due to prolonged immobility, drug treatment, and liver disease may all play a part.

Psychotic patients may suffer from malnutrition because they do not always eat the food presented to them. However, simple nutritional deficiency does not produce disturbances in the electrophoretic serum protein pattern,[6] nor is there reason to suspect that any of the patients were suffering from a malignant protein deficiency akin to kwashiorkor.

The general immobility which characterizes certain psychoses is not likely to be the cause of the abnormalities. They were no more severe in patients who had been in catatonic withdrawal for long periods of time (catatonic patients are likely to have the most severely disturbed physiology) than in other psychotic patients. In addition, a schizophrenic patient (patient G. A., Table 3), who was working full-time and was in apparently good present physical health, also had the line in the gamma globulin, elevation of macroglobulins (S19 = 533 mg. per 100 ml.), and the alpha$_2$ splitting.

Patients who had not been given ataractic drugs for at least two years had electrophoretic patterns comparable to those who had been given such drugs. We do not know, however, whether treatment in the distant past could have produced permanent globulin abnormalities. For example, insulin antibodies, resulting from the formerly fashionable insulin shock therapy, might have contributed to the hypergammaglobulinemia.

We think it unlikely that liver disease could be the cause of the hypergammaglobulinemia because, as previously stated,[1] (1) serum transaminase levels were almost all normal in the FII-positive group and were all normal in the FII-negative group, and (2) psychotic patients in a state hospital are presumably no more liable to cirrhosis of alcoholic or nutritional etiology than are prisoners in a Federal jail.

Nevertheless, we recognize that other important factors may cause the hypergammaglobulinemia. Patients in a state mental hospital often live in crowded conditions which may predispose to imperfect hygiene and to epidemics. Most of the sera used in this study were taken from patients living under seemingly good environmental hygienic conditions, at least half of them in special research wards. However, psychotic patients may have unhealthy personal habits, such as coprophagy, which could produce chronic infection and serum protein changes. We were not aware of such extreme habits in any of our patients. One cannot be certain, however, that such habits were not present in the past and were reflected later in biochemical disturbances in the serum. Finally, there were no prevalent epidemics at

the time of sera collection, and none of the patients had had documented infectious hepatitis to account for the hypergammaglobulinemia.

A curious finding, and one which we cannot explain, was splitting of the alpha$_2$ globulin. This was seen in 16 of 166 sera of psychotic patients and not once in the sera of the prisoners (Figures 2, 3, 4, and Table 3). It was seen most often (in six of 26 sera) in schizophrenics known not to have had ataractic drugs for two years. Nine of 84 FII-positive and one of 41 FII-negative sera showed the phenomenon. We were able to examine 10 of the 16 patients whose sera showed splitting of the alpha$_2$ globulin. The psychiatric diagnoses were: schizophrenic reaction, seven; psychotic depression, two; psychosis with epilepsy, one. Physical examination showed that three of the 10 had rheumatoid arthritis; the other seven had no apparent or significant organic disease. (It is of interest that we have since noted the same abnormality in the serum of an outpatient with rheumatoid arthritis who also had psychoneurotic depression.)

Reports have been made of similar findings in the alpha$_2$ globulin fraction in primary systemic amyloidosis,[7] fulminating viral hepatitis,[8] and obstructive jaundice.[9] Sunderman and Sunderman [10] saw 26 examples in the sera of 2,000 patients. They noted that seven of these patients had chronic myalgia, arthralgia, anemia, fever, emaciation, pleurisy, and dermatitis in the absence of any demonstrable etiologic agent. They made no mention of psychiatric disturbance.

Alpha$_2$ globulins comprise several immunologically distinct components;[11] the splitting implies that one or more of the components is present in increased quantity in these patients. Further observations are required to ascertain the significance of this increase.

Summary

The sera of 162 patients with chronic psychosis were subjected to electrophoresis on cellulose acetate. Qualitative abnormalities found were: (1) splitting of alpha$_2$ globulin in 16 (10%); (2) a sharp line superimposed upon the gamma globulin in 28 (17%); (3) an abnormally shaped gamma globulin curve, in the densitometric analysis, in 52 (32%). The main quantitative changes were (1) a mean hypergammaglobulinemia in all groups of patients, and (2) in some sera examined, a significant elevation of S19 macroglobulins.

The effect of chronic confinement, malnutrition, liver disease, ataractic drug therapy, and other factors coincidental to the psychosis in influencing serum protein changes were discussed. It was believed that some of these factors could be ruled out.

Other speculations about the significance of the findings included the possibility of the macroglobulin disturbance playing an important role in the pathogenesis of some psychoses.

More information is needed before the serum protein disturbance in chronic psychosis can be satisfactorily explained.

Acknowledgments

We are indebted to Dr. Alexander Simon for helpful comment, to Dr. Enoch Callaway, III, for invaluable criticism and encouragement, and to Mrs. Bernice Engle for help with the manuscript. John Koch gave very competent technical help, and Sanford Autumn made all the statistical calculations.

Summario in Interlingua

Microelectrophorese a acetato de cellulosa esseva effectuate in seros de 162 chronic patientes psychotic e 50 subjectos de controlo. Seros ab le sequente subjectos esseva usate: (1) 83 chronic patientes psychotic con seros continente factor rheumatoide, (2) 43 chronic patientes psychotic con seros sin factor rheumatoide, (3) 26 chronic patientes psychotic qui non habeva habite drogas ataractic depost duo annos, (4) 10 chronic schizophrenicos catatonic, e (5) 50 prisioneros a longe vista usate como subjectos de controlo.

Le resultatos in le 162 patientes psychotic esseva comparate con illos in le 50 prisioneros. Anormalitates qualitative esseva (1) fission de globulina alpha$_2$ in 16 casos (10%), (2) un linea imponite super le zona de globulina gamma in 28 (17%), e (3) un curva de conformation anormal pro globulina gamma in 52 (32%). Iste alterationes non esseva vidite in le seros del prisioneros. Le major anormalitates quantitative esseva (1) un moderate hypergammaglobulinemia in omne gruppos de patientes, (2) elevate macroglobulinas in 17 de 24 seros le quales habeva un linea in le zona de globulina gamma e le quales esseva examinate per ultracentrifugation analytic.

Le effectos producite in le proteinas seral per le confinamento chronic, le malnutrition, morbo hepatic, le therapia a drogas ataractic, e altere factores coincidente con le psychose es discutite. Es opinate que certes inter istos pote esser excludite.

Altere speculationes concernente le signification del resultatos include le possibilitate que le perturbationes del globulina gamma e del macroglobulina es importante in le pathogenese de certe psychoses. Le globulina gamma o le macroglobulina poterea haber un affinitate de typo anticorporee pro constituentes specific o metabolitos essential del cerebro. Lor presentia excessive in le sero poterea reflecter un processo auto-immun.

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THE DIFFUSE OBSTRUCTIVE PULMONARY SYNDROME IN A TUBERCULOSIS SANATORIUM. I. ETIOLOGIC FACTORS *†

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MORE than a hundred years ago Laennec described both tuberculosis and chronic obstructive emphysema, but without relating them to each other.[1, 2] Subsequently, a relationship between these disorders has been suggested by Anno and Tomashefski,[3] who showed a high incidence of pulmonary emphysema in selected tuberculosis patients, and by Gaensler and Lindgren,[4] who found obstructive pulmonary disease in 42.6% of 780 tuberculous patients who were being considered for surgery. The present study of a general tuberculosis population was initiated to define any relationship between the two diseases and to evaluate other factors of etiologic importance.

METHOD

The maximal expiratory flow rate [5] and the vital capacity were measured in each of the 710 patients admitted to Firland Sanatorium during the year ending October 1959. A trained technician questioned each person on historical points and symptoms. If the initial maximal expiratory flow rate had been abnormal, this variable was again tested and the patient's maximal breathing capacity and other pulmonary functions were measured after his acute symptoms had subsided. Data on the extent of the tuberculosis were obtained from the admission conference notes and from chest x-rays. All information was recorded on a special form and the data were then coded on IBM cards. The statistical methods used are described elsewhere.[6]

RESULTS

The diffuse obstructive pulmonary syndrome (DOPS) was found in 34% of the patients studied. The severity of the airway obstruction and the related symptoms are described elsewhere.[6] Historical factors related to the incidence of obstruction are discussed below.

Sex: Among the 509 men in the group, 184 (36%) had obstructed flow, and obstructed flow occurred in 57 (28%) of the 201 women. This sex difference is not significant ($p > 0.05$).

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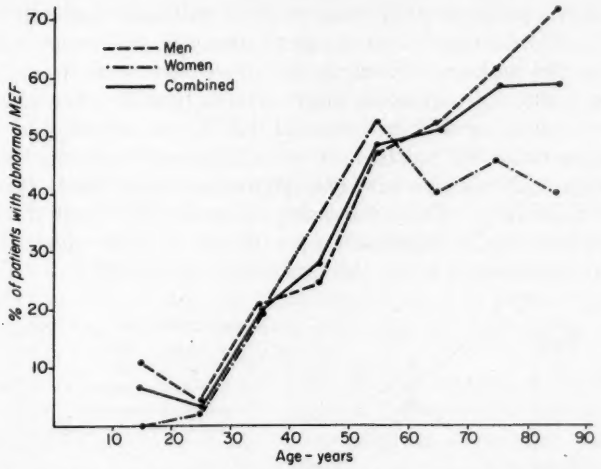


FIG. 1. Relationship of age and maximal expiratory flow in 710 admissions for tuberculosis.

Race: Most of the patients were of Caucasian extraction, although Negro, Oriental, American Indian, Mexican, Eskimo, Filipino, and other groups were represented. The incidence of obstructive pulmonary disease was lower in non-Caucasians, but when the data were corrected for age the difference between ethnic groups disappeared ($p > 0.05$).

Age: Figure 1 illustrates the increased incidence of abnormal flow rates with advancing years. The relationship between maximal expiratory flow (MEF) and age is significant ($p < 0.001$) and correlates well ($r = -0.489$ male, -0.506 female).

Tuberculosis Diagnosis: Figure 2 shows the relationship between obstructed flow rates and the extent of tuberculosis. Minimal tuberculosis

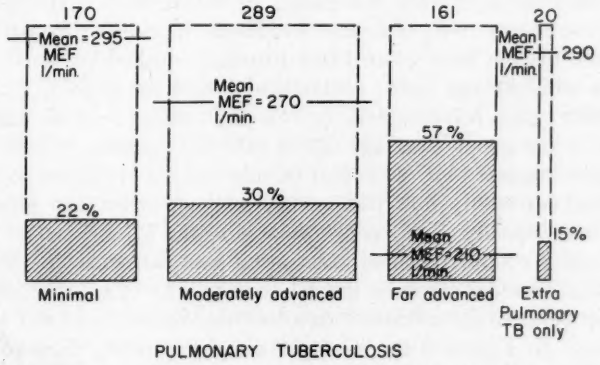


FIG. 2. Relationship of extent of tuberculosis and expiratory flow rate.

occurred in 170 patients; 37 of these (22%) had abnormal MEFs (group mean MEF, 295 L./min.). Moderately advanced pulmonary tuberculosis occurred in 289 patients. Evidence of airway obstruction was found in 87 of these (30%; group mean MEF, 270 L./min.). Far advanced tuberculosis occurred in 161 patients, 92 (57%) of whom had abnormal MEFs (group mean MEF, 210 L./min.). Obstruction of the airways was found in 15% of 20 patients with extrapulmonary tuberculosis (group mean MEF, 290 L./min.). The relationship between MEF and the extent of tuberculosis was highly significant ($p < 0.001$). (The other 70 patients had inactive tuberculosis or another pulmonary disease.)

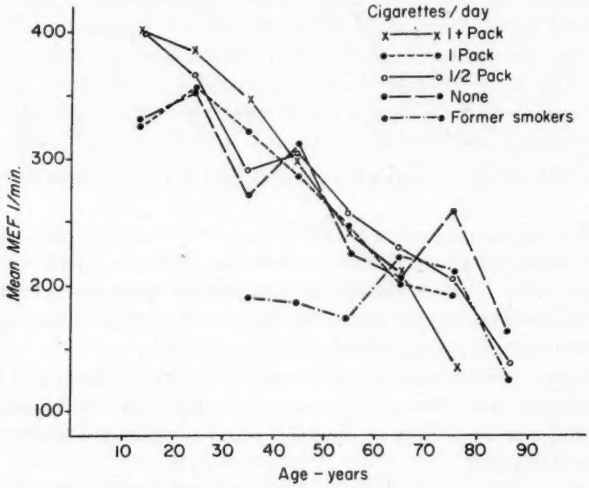


FIG. 3. Relationship of smoking habits and maximal expiratory flow rate.

The relationship between the extent of tuberculosis and the incidence of the diffuse obstructive pulmonary syndrome would be affected by age if far advanced disease were more likely to occur in older persons. Tests of association with the age factor controlled showed the degree of association highest in the group below age 40 ($r = -0.54$ males, -0.80 females) and the lowest in the group over age 60 ($r = -0.24$ males, -0.35 females). These results suggest that the extent of tuberculosis is related to an abnormal maximal expiratory flow particularly in the younger age group.

Since vital capacity (VC) is also related to the MEF [6] and to the extent of tuberculosis, a similar test of association was performed on the relation of MEF and tuberculosis with the VC controlled. This test affirmed the relationship between far advanced tuberculosis and an abnormal MEF.

Smoking: In Figure 3 the mean maximal expiratory flow for smokers and nonsmokers is plotted against age in years. One hundred thirty patients

were nonsmokers, 147 smoked no more than 10 cigarettes a day, 281 smoked 10 to 20 cigarettes, and 73 smoked more than 20 cigarettes a day. Thirty-two patients had stopped smoking at least two years before being examined; the remaining patients used other forms of tobacco. The number of cigarettes smoked was not significantly related to abnormal MEF ($p > 0.05$). Lack of relationship was also found in those using other forms of tobacco. In one group, comprising men less than 59 years old who had stopped smoking two or more years before, the incidence of abnormal MEFs was significantly high ($p < 0.05$), but no such relationship occurred in older men or in women who had stopped smoking.

The duration of smoking in years appeared to be significantly related to the incidence of DOPS; however, when the age factor was controlled, the relationship was no longer significant.

Occupation: Seven specific and four general categories [7] based on exposure to dusts, fumes, and smoke were used to evaluate any influence of occupation on the incidence of the diffuse obstructive pulmonary syndrome. Airway obstruction occurred in 62% of patients who had worked at metal mining, coal mining, or with stone products. This incidence was significant ($p < 0.01$) but the correlation was poor ($\lambda b = 0.043$). The duration of exposure to a given dust was not significant.

No significant differences in the incidence of DOPS occurred among patients whose occupations were classified in general terms as business, professional, clerical, skilled labor, unskilled labor, students, housewives, and miscellaneous. Those in business, professional, and skilled labor positions appeared to have a higher incidence of DOPS, but when the data were corrected for age the significance disappeared.

Residence: The place of residence, urban or rural, and the portion of a lifetime spent in either location were coded. An urban area was defined as a population center with at least 10,000 inhabitants, or a smaller town with an industrial installation. Ten groupings were made on the basis of the sequence and time of residence. No grouping, or meaningful combination of groups, was related to the incidence of DOPS.

Asthma: A history typical of asthma was obtained for 67 patients, 46 (68%) of whom had obstructed flow rates. This incidence is significantly greater than that in the general study population ($p < 0.001$); however, the predictive efficacy of this factor was poor ($\lambda b = 0.087$ male, 0.215 female). The age at which the asthma began and its duration were not significantly related to the incidence of the diffuse obstructive pulmonary syndrome. These figures do not include those patients who considered their present symptoms to be "asthma."

Allergies Other than Asthma: A history of allergies (hives, dermatitis, hay fever, or drug sensitivity) was not associated with any increase in the incidence of diffuse obstructive pulmonary syndrome.

Family History of Allergies or Pulmonary Disease: No family history

of emphysema, asthma, hay fever, dermatitis, bronchitis, bronchiectasis, nonspecific pulmonary disease, tuberculosis, or a combination of these diseases appeared to be significantly related to the incidence of DOPS.

Past Medical History: Abnormal flow rates were not related to a history of pneumonia, influenza, pertussis, head colds, or sinusitis. Because alcoholism is common among patients in tuberculosis sanatoria, this parameter was recorded but was found to be of no significance. Of the patients reporting three or more chest colds, each lasting a week, every winter, 51% had obstructed airways ($p < 0.001$). The correlation with obstructive airway disease was low because the number involved was relatively small.

Other Diseases: One hundred disease categories were surveyed to discover any relationship between the diffuse obstructive pulmonary syndrome and other diseases existing at the time of admission. Organic heart disease, whether compensated or decompensated, was associated with a higher incidence of obstructive pulmonary diseases. However, such patients were older persons and when the age factor was controlled this significance disappeared.

Twenty patients had primary pulmonary malignancies. MEFs indicating obstructive disease were present in 65%; 25% could not perform the test. Even when the ages of these patients are taken into account, the incidence is much higher than would be expected ($p < 0.05$).

Peptic ulcer (active, inactive, or treated by gastrectomy) was not associated with an increased incidence of DOPS. Of 47 patients with such a condition, 16% had obstructed airways. Conversely, 12 (5%) of the 241 patients with airway obstruction had an ulcer, but 35 (7%) of the 469 patients without evidence of obstruction gave a history of peptic ulcer.

DOPS occurred in 17 (56%) of 30 patients with silicosis. Even after correction for other variables, this incidence is significant ($p < 0.01$).

Thoracic Surgery or Alteration: Ninety-five patients had pleural disease of varying severity with or without parenchymal disease, four had unilateral diaphragmatic paralysis, and 64 had had resectional surgery, thoracoplasty, or both. Over 50% of this group had obstructed airways. When the factor of vital capacity was controlled, the incidence of obstruction was not significant ($p > 0.05$). Thus the incidence of a reduced maximal expiratory flow in this group can be considered significant only if it is assumed that the reduction in vital capacity was more a reflection of the diffuse obstructive pulmonary syndrome than of the thoracic alteration.

Discussion

The relationship between age and incidence of obstructive pulmonary disease might be expected. It is common clinical experience that the incidence of DOPS rises sharply in patients over 40. This observation has contributed to the thinking of some that this is a disease of disuse [8] or overwork.[9] Because the age factor is significant the disease has sometimes been

considered to result from "wear and tear" or to be a degenerative condition.

A specific relationship between DOPS and the extent of pulmonary tuberculosis has not been described previously, although Gaensler and Lindgren [4] reported that 42.6% of their patients with moderate or far advanced pulmonary tuberculosis had emphysema by functional criteria. In the present study 39% of the patients with this degree of disease had airway obstruction. Current theories on the etiology and pathogenesis of emphysema that are applicable in relation to the extent of tuberculosis are: (1) chronic recurrent bronchial infection; (2) chronic trauma due to severe coughing; (3) inflammatory swelling of the bronchial mucosa and/or impairment of ciliary action; and (4) premature aging.[10] Routine bronchoscopy in tuberculosis does not often reveal tuberculous or nonspecific bronchitis in the visible tracheobronchial tree. If either condition is present, it must be in the smaller airways. With improvement and reduction in sputum, amelioration of the DOPS would be expected. No such change was found in 30 patients after a period averaging eight months. Although values fluctuated from patient to patient, no mean change in MEF, MBC or vital capacity occurred.[9]

The relationship of lifelong trauma to the development of DOPS remains speculative. Tuberculosis adds cough, to traumatize the lung further. Infection and scarring are also added. These insults to the lung tissues may cause a change in the mechanical properties of the lung, such as loss of elastic recoil, and may result in obstructive airway disease. Whether these changes result in premature aging of the lung is unknown, but additional investigation seems to be warranted to establish the relationship between the extent of tuberculosis and the diffuse obstructive pulmonary syndrome.

Bell [11] has shown that tuberculosis in the rabbit can lead directly to the production of dilated lung spaces, and bullae have been observed in association with tuberculosis in man.[12, 13] There is little other pathologic evidence indicating a granulomatous etiology of DOPS.

Questions to provide information on the possibility that tuberculosis may predispose to emphysema or vice versa were incorporated in this study when it became evident that the association existed. From the history and clinical data an attempt was made to determine whether tuberculosis or DOPS had temporal precedence. For half the patients no such decision could be made, and the remaining patients were equally divided among those who had tuberculosis first and those who had a preceding diffuse airway obstruction.

It is possible that tuberculosis is more likely to develop in the patient with chronic DOPS and to reach greater severity before he becomes sufficiently alarmed to seek medical attention. In the advanced cases of emphysema pre-existing symptoms of respiratory infection, cough, shortness of breath, and fatigue, would differ little from those produced by tuberculosis. Obstructive emphysema, being a disease of abnormal ventilation to perfusion

ratios, produces pulmonary areas with high alveolar oxygen concentrations. These areas will allow greater mycobacterial growth. If such were the case and these were the large spaces seen pathologically, tuberculosis would be expected to develop in those areas showing a predilection for emphysema. McLean [14] has stated that the transition of a centrilobular to a diffuse emphysema pattern usually occurs first in one part of the lung and most often in the upper lobe. This would coincide with the usual location of adult tuberculosis. Thus in the pathologic specimens described as having emphysema around a tuberculous lesion, the emphysema might have had temporal precedence.

Absolute lack of confirmation of certain factors heavily stressed by other authors discussing the production of DOPS is an unexpectedly prominent result of this study. Chronic bronchitis, prevalent in Great Britain, has been equated by some authors with emphysema, as reported in the United States. Fletcher [15] and Higgins [16] report a ratio of men to women as high as four to one in chronic bronchitis. Gaensler and Lindgren [4] noted a ratio of 3.76:1 in 100 cases of emphysema in the United States. In each of these studies there has been a selection of cases based on geography, occupation, extent of tuberculosis, et cetera. In patients coming from the areas supplying the tuberculosis admissions to Firland Sanatorium there is no sex-related difference in the incidence of DOPS.

The mean mortality from chronic bronchitis has been reported to be two or three times greater in those who resided in cities rather than in the country.[15] In the present tuberculosis population no influence of urban or rural living upon the incidence of airway disease was found. This finding is in keeping with the comparison made by Higgins [16] between an agricultural valley and an industrial area with high air pollution. The nonminers in the industrial environment had symptoms and disabilities similar to those of the residents in the agricultural community. This demonstrates the importance of occupational exposure rather than that of atmospheric pollutants in general.

Our survey agreed with other studies, showing that patients who had once been miners had a significantly higher incidence of DOPS.[16] No association between skilled or unskilled labor, indoor or outdoor work, or sedentary or active occupations could be demonstrated. This result is contrary to Fletcher's study [15] of chronic bronchitis in England. He found that it affects laborers five times as often as it does the managerial class, and described it as a disease of the social strata. Pemberton [18] has pointed out that social differences are not as apparent in the United States as they are in Great Britain, and the present findings correspond with his and with those of Motley [19] in the United States. The significant occupational relationship of DOPS and mining in this study is particularly evident in the patients with silicosis who have a high incidence of DOPS.

Of the other disease states pulmonary malignancies were associated with

a significantly higher incidence of the diffuse obstructive pulmonary syndrome. Contrary to other studies,[20, 21] peptic ulcer was not related to the incidence of DOPS. As gastrointestinal x-rays were not performed on every admission, the present results reflect the information obtained by the interrogator, in combination with the clinical history and physical examination as recorded on the patient's chart. It has been stressed in other studies that peptic ulcer in emphysema is often silent. Thus, this relationship may have been missed.

Association between smoking and chronic bronchitis has been reported from England [16] and between smoking and emphysema in the United States.[22] In this country, studies using the same screening apparatus as in the present study have borne out the association of smoking and DOPS.[23] Physiologic studies by Wilson and his co-workers [24] have confirmed the existence of small but significant differences in various measurements of pulmonary function between smokers and nonsmokers. In tuberculosis patients admitted to Firland Sanatorium, the flow rates of smokers and nonsmokers do not differ as a result of either the amount or the duration of smoking. The one group having more DOPS comprised men below the age of 59 who had ceased smoking two or more years before. Were advancing symptoms of this disease enough to warrant giving up the habit? Certainly in the older age group, those who had ceased smoking had no greater frequency of the diffuse obstructive pulmonary syndrome. Perhaps the small differences between smokers and nonsmokers shown by others become insignificant in the presence of a major condition such as tuberculosis.*

Recent investigations have shown a high sweat chloride content in many individuals with emphysema, and in their relatives. This finding is also associated with consanguinity of children having mucoviscidosis and has led to the assumption that many cases of emphysema are formes frustes of mucoviscidosis.[25] If mucoviscidosis were a significant factor in the production of DOPS, correlation with a family history of respiratory disease or emphysema should have been found. The findings presented agree with those of Hurst,[26] who found no familial factor for emphysema or for the "chronic bronchitis syndrome." If mucoviscidosis were a significant factor, we might also expect a long personal history of bronchitis, asthma, frequent respiratory infections, sinusitis, et cetera. Such findings would also be supported by the suggestions of Leopold and Gough [27] and by those of McLean [28] that a bronchiolitis or a peribronchiolitis is the initial lesion in emphysema. A history of bronchial asthma was associated with a higher incidence of DOPS. Chest colds of long duration or great frequency

* On a topic such as smoking it is difficult for the examiner to avoid injecting bias into the study. In the present investigation all information was obtained from the patient by a technician who had no preconceived notions regarding the associations between the tests and the habit. Abnormal function tests were rechecked by other technicians unaware of the patient's smoking history. The bias on the part of the authors prior to the study would have been to indict tobacco as contributing to airway obstruction.

were also related. Other respiratory infections or inflammations were not significant.

Search for etiologic factors common to all cases of the diffuse obstructive pulmonary syndrome may be unrealistic if several disease states have in common airway obstruction.

Summary

The diffuse obstructive pulmonary syndrome, as determined by a measurement of the maximal expiratory flow rate, was present in 34% of the patients admitted to a tuberculosis sanatorium in a one-year period. The most significant factors associated with this incidence were age and severity of tuberculosis. Patients with bronchial asthma, pulmonary malignancy, frequent protracted chest colds, and clinical evidence of silicosis had a significantly high incidence of the diffuse obstructive pulmonary syndrome. The sex or race of the patient was not related. The influence of tobacco habits, residential history, family history, and the past medical history of allergies, chronic sinusitis, peptic ulcer, pneumonia, influenza, pertussis, or head colds was negligible.

Summario in Interlingua

Le patientes in 710 consecutive admissiones in un sanatorio de tuberculose esseva interrogate con respecto a lor symptomas e lor antecedentes medical. Esseva determinate in omne le casos le maximo del fluxo expiratori e le capacitate vital. Si le fluxo o le volumine esseva anormal, plus complete studios esseva effectuate in le laboratorio de function pulmonar.

Trenta-quatro pro cento del patientes in iste admissiones pro tuberculose habeva morbo obstructive del vias aeree. Le plus significative factores associate con iste incidentia esseva le etate del patientes e le severitate del tuberculose. Vinti-duo pro cento del patientes con grados minime de tuberculose, 30% del patientes con moderatemente avantiate formas de tuberculose, e 57% del patientes con avantiatissime tuberculose habeva anormalitates del fluxo expiratori.

Patientes con asthma bronchial, malignitate pulmonar, frequente e prolongate episodios de catarrho thoracic, e evidentia clinic de silicosis habeva un significativemente elevate incidentia del diffuse obstructive syndrome pulmonar. Sexo e racia non esseva correlationate con le condition. Le influentia de habitudes nicotinic, del antecedentes residential, del anamnese familial, e del antecedentes medical de allergia, sinusitis chronic, ulcere peptic, pneumonia, influenza, pertusse, o catarrhos de capite esseva negligibile.

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THE DIFFUSE OBSTRUCTIVE PULMONARY SYNDROME IN A TUBERCULOSIS SANATORIUM. II. INCIDENCE AND SYMPTOMS*†

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IT is increasingly evident that a diffuse obstructive pulmonary syndrome is often associated with tuberculosis.[1, 2] A considerable number of patients in sanatoria require treatment for chronic obstructive pulmonary emphysema as well as for tuberculosis, and deaths in these institutions now occur more often from emphysema than from progressive tuberculosis. This study was initiated to determine the prevalence and severity of obstructive airway disease among patients admitted to Firland Sanatorium.

METHOD

During the year ending October 1959, a trained technician questioned the 710 patients who were at least 16 years old and who were admitted for the first time concerning pertinent historical points and symptoms. The vital capacity was measured, and the maximal expiratory flow rate was ascertained with the "puffmeter" described by Goldsmith.[3] The mean of the three best values of five for the maximal expiratory flow was recorded. If the flow rate or volume was abnormal, the patient's condition was evaluated in the cardiopulmonary laboratory, where the maximal breathing capacity with and without bronchodilators, the maximal expiratory flow, and the vital capacity were measured. When indicated, the oxygen saturation, carbon dioxide content,[4] and pH of the arterial blood were measured. The P_{CO_2} was calculated from a Singers-Hastings nomogram.[5]

Data on the extent of the tuberculosis and on the secondary diagnoses were taken from the clinical charts. X-rays were read with special attention to the extent of tuberculosis and to any evidence of emphysema. The information was recorded on punched cards § and was subjected to statistical analysis by use of the chi-square test,[6] and by tests of correlation[7] and association.[8]

Since the flow rates and volumes might change with a clearing of the tuberculosis, or as a result of a reduction in sputum, cough, and toxicity,

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30 patients studied soon after admission were again studied eight months later. Although changes occurred in some patients, these were random, and no significant changes in the mean expiratory flow or vital capacity occurred in the group as a whole.

Results

Flow Rates: Normal expiratory flow rates ascertained by the method used exceed 260 L./min. for men and 210 L./min. for women.[3] In 241 patients (34% of the group) the maximal expiratory flow (MEF) was below these levels. In 51 patients (7%) the MEF was not measured because they were physically or mentally unable to cooperate.

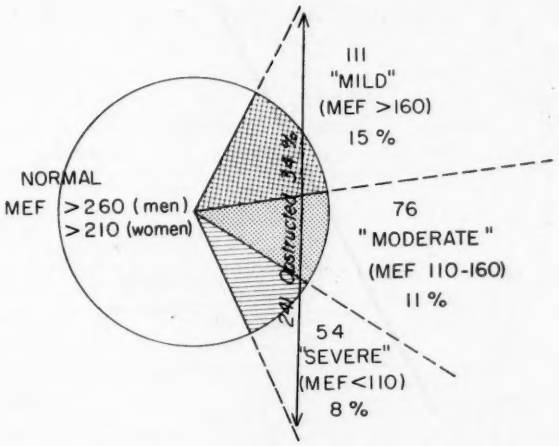


Fig. 1. Incidence of abnormal expiratory flow rates in tuberculosis patients.

In 111 patients (15%) the obstructive airway disease was mild; the maximal expiratory flow was above 160 L./min. but below the normal values (Figure 1). These patients were for the most part asymptomatic. Moderate obstruction (MEF, 110 to 160 L./min.) was present in 76 patients (11%), and in 54 patients there was severe obstruction, MEF being less than 110 L./min.

The maximal breathing capacity (MBC) was measured in 168 of the 241 patients with low MEFs (Figure 2). The maximal breathing capacity correlated well with the maximal expiratory flow ($r = 0.768$ for males, 0.845 for females). In 102 patients the MBC was again measured after administration of a bronchodilator aerosol (Aerolone Compound). In 70% of these the rise in the predicted maximal breathing capacity[9] was less than 12%. The change in MBC with administration of bronchodilators was not related to the severity of the airway obstruction.

Vital Capacity: The vital capacity (VC) was significantly related to the maximal expiratory flow ($r = 0.755$ for males, 0.671 for females). Additional study of this relationship showed that normal individuals with a vital capacity of 2 L. or more can produce a normal MEF. Five men and 14 women had a VC of less than 2 L. Correction for these few cases made little difference in the incidence.

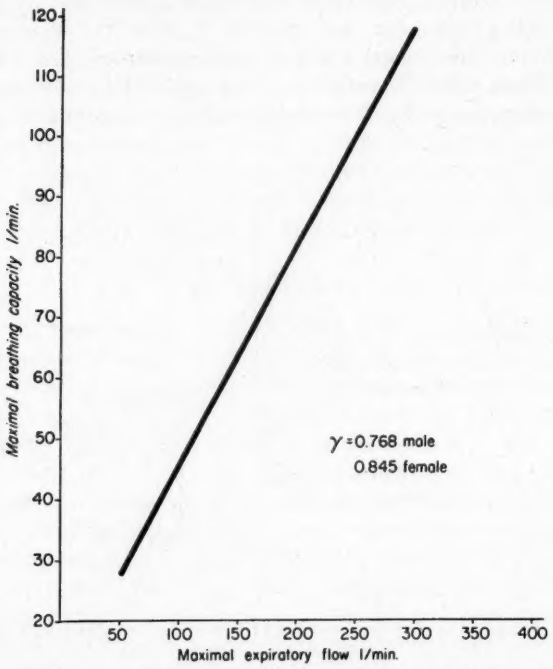


FIG. 2. Relationship of maximal breathing capacity and maximal expiratory flow rate.

Blood Gas Content: Blood gas analysis was performed consistently only on those patients with an MEF of less than 110 L./min. An arterial oxygen saturation of 94% or lower was found in 31 patients (4%). Certainly this must be the lowest incidence of hypoxia possible in this population. In eight male patients (1.1%) the arterial P_{CO_2} was greater than 49 mm. Hg.

SYMPTOMS

Dyspnea: On the basis of the New York Heart Association classification of functional capacity,[10] dyspnea was coded from 0 to IV. Table 1 shows the correlation between the symptom (dyspnea) and the MEF ($r = -0.689$ for male and female). Among the historical points used to classify the

degree of dyspnea, the single exercise best correlated with the maximal expiratory flow was the number of stairs climbed before the onset of dyspnea ($r = 0.528$ for males, 0.428 for females). Only one of 25 men having severe diffuse obstructive pulmonary syndrome (DOPS) or an MEF below 110 L./min. had no complaint of shortness of breath. This group averaged 10 stairs before onset of dyspnea. Men with moderate, diffuse obstructive pulmonary syndrome or with an MEF between 110 and 160 L./min. averaged 20 stairs before the onset of shortness of breath. Ten (23%) of this group denied having dyspnea. Men with mild DOPS averaged 30 steps before the onset of shortness of breath, and 65% denied having exertional dyspnea.

TABLE 1

RELATIONSHIP OF DYSPNEA AND ABNORMAL FLOW RATES
(men and women)

Flow Rates	No Dyspnea (0) or Unknown	Mild Dyspnea (I)	Moderate Dyspnea (II)	Severe Dyspnea (III)	Incapacitating Dyspnea IV
Normal	324	101	27	10	7
Abnormal	73	75	41	44	8
% Abnormal Flow Rates	18	43	60	82	53

The duration of dyspnea correlated poorly with the incidence of an abnormal MEF ($r = -0.176$ for males, -0.184 for females), but the trend indicated that the longer one had had dyspnea the more likely he was to have an abnormal maximal expiratory flow.

Cough: The number of years during which patients experienced symptomatic cough was unrelated to the incidence of airway obstruction. The probability of an abnormal MEF increases with the severity of the cough ($\gamma = 0.40$). Mild cough was defined as one occurring once or twice daily, or as "smoker's cough," and moderate cough as one occurring several times daily. The incidence of obstruction was 50% among patients suffering from severe cough, which was defined as one occurring at least once an hour or awakening the patient at night. During the test of the maximal expiratory flow 30% of those with abnormal values and 13% of those with normal flows coughed.

Sputum: The nature of the sputum was classified as clear and thin, mucoid, or purulent. The probability of abnormal flow rates was greatest for those with purulent sputum ($p < .01$). The volume of sputum was divided into three categories: less than two tablespoonfuls daily, two to four tablespoonfuls daily, and more than four tablespoonfuls daily. Patients who raised more than four tablespoonfuls of sputum daily had a higher incidence of abnormal flow rates, and this was true even after the nature of the sputum was controlled ($p < .05$). The predictability of an abnormal MEF from knowledge of the volume and nature of the sputum, however, was poor ($\lambda ab = 0$). This does not indicate a lack of association, but indicates a lack of predictive efficiency of the variable character of sputum.

Dizziness and Syncope; Clubbing and Cyanosis: Dizzy spells or syncope occurring with cough or exertion were experienced by 14% of the patients with the diffuse obstructive pulmonary syndrome and by 6% of those without airway obstruction ($p < .01$). Occurrence of these symptoms without cough or exertion had no significance. Again, the predictability of an abnormal MEF from knowledge of this parameter was poor ($\lambda ab = 0.137$).

The incidence of obstruction was 70% in patients who showed clubbing of the fingers, and was 66% in those with occasional or constant cynanosis. However, the number of patients with these symptoms was small; only 3% of the patients with airway obstruction showed clubbing and only 4% had cyanosis.

Orthopnea: Seventy-two per cent of the patients with orthopnea had DOPS ($p < 0.001$). Of the patients mentioning paroxysmal nocturnal dyspnea, 75% had airway obstruction. The incidence of obstruction was similar in those complaining of both orthopnea and paroxysmal nocturnal dyspnea ($p < 0.001$).

Swelling of the ankles was reported by 25 patients, 15 of whom had the diffuse obstructive pulmonary syndrome ($p < 0.01$).

X-ray Findings: The extent of tuberculous involvement that was visible on x-ray film correlated moderately well with the MEF ($r = -0.404$ for male, -0.46 for female).

Chest x-rays showing a large chest volume, a flattened diaphragm, hyperlucent lung fields, and a small heart (signs usually considered diagnostic of emphysema) were present in 49 cases. Abnormal flow rates were also present in 35 of these. In seven the maximal expiratory flow could not be measured because of patient illness or uncooperativeness. X-ray findings suggestive of emphysema (by any two of the above criteria) were present in 67 cases and were accompanied by reduced MEFs in 31. Two patients in this group were unable to perform the tests. Despite these findings the correlation between an x-ray reading of emphysema and an abnormal MEF indicates little ability to diagnose airway obstruction from x-ray films ($\lambda b = 0.07$ for female, 0.14 for male).

The presence of diffuse pumonary densities was not associated with a significantly increased incidence of reduced maximal expiratory flows.

Discussion

The incidence of emphysema reported in various papers seems to be dependent upon case-finding methods and upon the definition of the condition. Anderson[11] reports an incidence of 2 to 5% in autopsy cases. McLean,[12] who used the criteria of pathology, reports a 6.7% incidence. Anno and Tomashefski[1] found a maximal breathing capacity below normal values in 25% of selected cases with moderately advanced tuberculosis, and half of their patients with far advanced tuberculosis had an abnormal MBC. Using physiologic criteria, Gaensler and Lindgren[2] found obstructive pulmonary disease in 42% of tuberculosis patients who were being considered for surgery, and Brinkman and Coates[13] have shown that 50% of the men between the ages of 60 and 65 years in an industrial population had obstructive airway disease. The results of the present study are in keeping with the physiologic reports and show that 34% of 710 patients admitted for active tuberculosis also had the diffuse obstructive pulmonary syndrome. However, the distribution of this population with respect to age and sex was skewed. Whether this incidence applies to a general population is not known. The percentage may be lower than that reported by Gaensler and Lindgren because they studied only patients with moderate or far advanced tuberculosis. The relationship of the extent of tuberculosis and the incidence of DOPS will be discussed elsewhere.[14]

The incidence of emphysema in autopsy material is significantly lower than the incidence of airway obstruction indicated by physiologic studies. It seems likely that the DOPS of the physiologist shows other than the typical pathologic picture of emphysema.[15] Not only may patients with mild obstruction fail to show architectural change; patients in similar end stages physiologically may show varied anatomic pictures.

The test of the maximal expiratory flow used in this study has proved to be a helpful measure by a sturdy case-finding tool. The relationship of the MEF to the MBC (Figure 2) has a correlation of 0.95 according to Goldsmith[3] and slightly less in the present study ($r = 0.768$ to 0.845). Measurement of the maximal expiratory flow would appear to be a more sensitive indicator of obstructive airway disease than that of the maximal breathing capacity. The test of the MEF is simpler, more patients perform it well, and, in this study, it did not seem to be affected by the toxicity that accompanied tuberculosis. Repetition of the MEF and VC measurements eight months after admission showed no significant difference in mean values in 30 patients.

The correlation between the vital capacity and the maximal expiratory flow observed in this study clearly relates lung volume and this measurement of flow rate. The facts that a 2 L. vital capacity in normal subjects

allows an MEF in the normal range, and the small number of cases with a VC less than 2 L. in this study made us confident that we were measuring airway obstruction. The fact that the VC does decrease in severe obstructive disease without other evidence of restriction also would result in a positive correlation between vital capacity and maximal expiratory flow.

The severity of the diffuse obstructive pulmonary syndrome in these patients is demonstrated by the fact that 54 had an MEF below 110 L./min. Thirty-one had an arterial oxygen saturation of 94% or lower and eight had carbon dioxide retention. As a result, arterial blood gases are routinely studied in all patients in this sanatorium who have an MEF below 110 L./min. in the anticipation that over half of them will show hypoxia.

That the MEF is a measure of disability is seen in Table 1. The correlation between dyspnea and MEF is high (> 0.688) and is close to that obtained in objective testing of the same parameter (MBC). The duration of dyspnea was hardly related to the incidence of abnormal flow rates.

In England the nature and volume of sputum have been considered to be significantly related to the incidence of chronic bronchitis.[16] When these criteria are compared with pulmonary function studies a relationship is found between airway obstruction and the nature and volume of sputa. Those patients who produce more than four tablespoonfuls of a purulent sputum daily have a significantly higher incidence of DOPS. Correlation of volume and nature of sputa with MEF was zero, however, making the predictive efficacy of this variable worthless.

Similarly relating chronic bronchitis and the diffuse obstructive pulmonary syndrome (functional designation) is the relationship of cough to the incidence of both. The severity of cough was significantly related to a higher incidence of DOPS, although the duration of cough was not so related.

Patients reporting dizzy spells or syncope, with cough or on exertion, clubbing of the fingers, cyanosis, orthopnea, and swelling of the ankles had a significantly higher incidence of DOPS. The small numbers involved, however, made the predictive efficacy of these signs poor.

X-ray abnormalities interpreted as being those of emphysema had a significant association with the diffuse obstructive pulmonary syndrome, but the proportion of cases who showed abnormal roentgen findings and flow rates was very small. The low proportion might be due to the finding of obstruction by the flow test before rarefaction of pulmonary parenchyma or residual volume increase had occurred to give the classical x-ray evidence of emphysema. The finding would lead one also to believe that there are other states resulting in airway obstruction in addition to that typically described as large thorax, hyperlucent lung fields, small heart, and low diaphragm. The poor possibility of predicting functional disability from chest x-rays has been noted by others.[17, 18]

The failure of x-ray and pathology to detect DOPS lends further

credence to the concept that obstructive airway disease does not always have the typical anatomic picture of emphysema. Several etiologies and architectural pictures may be related to DOPS, and may be functionally indistinguishable.

Dyspnea was the most valuable symptom in the diagnosis of DOPS. Severe cough was of moderate value and no other symptoms were useful. Fletcher[19] has pointed out that cough and sputa are the symptoms of a pre-existing bronchitis (or tuberculosis in this study) and of little aid in the diagnosis of obstructive emphysema. Physical examination and x-ray of the chest similarly have a limited value in case findings. Adequate diagnosis can be accomplished only by using physiologic methods.

Summary

One-third of the adults admitted to a tuberculosis sanatorium in one year had obstructive airway disease: 8% had severe obstruction, 11% had moderate obstruction, and 15% had mild obstruction. The symptoms most closely related to obstructed flow rates appear to be dyspnea and severity of cough. The nature and volume of sputum, syncope, and dizziness on cough or exertion, orthopnea, swelling of the ankles, and cyanosis were significant, but they appeared in so few of the patients with reduced expiratory flow as to be of little diagnostic value.

An x-ray diagnosis of emphysema is well correlated with the diffuse obstructive pulmonary syndrome but can be made in such a small number of the cases of obstructed flow that it is useless in case finding.

Measurement of the maximal expiratory flow rate is a useful tool in determining diffuse obstructive pulmonary disease. This test correlates well with the maximal breathing capacity and with the symptom of dyspnea, and can be performed by many more individuals.

Acknowledgment

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Summario in Interlingua

Esseva interrogate 710 consecutive novemente admittite patientes de un sanatorio de tuberculose con respecto a symptomas e altere informationes anamnestic de interesse ab le puncto de vista de morbo obstructive del vias aeree. Le maximo del fluxo expiratori e le capacitate vital esseva determinate. Si le fluxo o le volumine esseva anormal, le patiente esseva re-examinate per medio de plus complete studios in le laboratorio de function pulmonar.

Un tertio del 710 patientes adulte habeva morbo obstructive del vias aeree. In 8% le obstruction esseva sever o le maximo de fluxo expiratori esseva minus que 110 L per minuta. In 11% le obstruction esseva moderate o le maximo de fluxo expiratori esseva inter 110 e 160 L per minuta. In 15% le obstruction esseva leve o le maximo de fluxo expiratori esseva plus que 160 L per minuta sed minus que la

norma. Le symptomas relationate le plus intimemente con anormalitate del fluxo pareva esser dyspnea e severitate de tusse. Le natura e le volumine del sputo, syncope e vertigine post tusse e effortio, orthopnea, tumescentia del region malleolar, e cyanosis esseva significative, sed illos esseva presente in un numero si basse del patientes con reducite fluxos expiratori que illos habeva pauc valor diagnostic. Un diagnose roentgenologic de emphysema es ben correlationate con le diffuse obstructive syndrome pulmonar, sed illo pote esser establite in un si basse numero de casos con obstruction del fluxo expiratori que illo perde omne valor in le detection de casos.

Le mesuration del maximo de fluxo expiratori es un methodo utile in deteger le diffuse obstructive syndrome pulmonar. Iste parametro es ben correlationate con le maximo del capacitate respiratori. Illo pote esser determinate per un multo plus grande numero de individuos, e illo es ben correlationate con le symptoma de dyspnea.

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THE ROLE OF LEUKOCYTE AND PLATELET ANTIBODY TESTS IN MANAGEMENT OF DIVERSE CLINICAL DISORDERS * †

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IT has been known for more than 50 years that heterologous platelet antibodies can induce experimental thrombocytopenic purpura[1-3] and that iso-immune leukocyte antibodies can lead to pyrogenic and urticarial transfusion reactions.[4] Yet surprisingly little attempt was made to transfer these concepts to clinical states of leukopenia and thrombocytopenia until Oliva and Burbetta[5] in 1944 and Evans et al.[6] in 1948 showed in vitro evidence of cytotoxic substances in plasma, and Harrington et al.[7] shortly thereafter found profound in vivo thrombocytopenic activity of plasma from a patient with idiopathic thrombocytopenic purpura.

These latter studies were soon followed by the development of a number of tests designed to study the clinical incidence of such immune substances. These tests fell into three general categories: a modified Coombs type of platelet testing, including consumption of antiglobulin in the serum, by Moulinier,[8] Fleuckiger et al.,[9] Jaeger et al.,[10] and Stefanini et al.;[11] the presence of macroscopic aggluination on mixing unknown sera with specific cells as developed principally by Dausset and Malinvaud[12] and Harrington;[13] and the quantitative micro-methods developed in this laboratory.[14-17] More recently, Dausset et al. proposed another variation of the antiglobulin consumption test in an effort further to increase the detection of the autoimmune antibodies.[18] The application of these various tests in different laboratories led to conflicting results, which in part were due to the complexity of the serologic methods and in part due to interpretation of data. The subject was further confused by the fact that some of the workers were studying normal sera obtained from blood bank samples, whereas other workers were studying abnormal sera primarily obtained from hematologic clinics. Slowly but surely these differences in technic are being resolved, with increasing agreement in results. This development has been due chiefly to realization of the importance of such simple but often overlooked factors as properly collected blood specimens, free of lipids or bacterial contamination; removal of all coagulation proteins with which platelets

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normally interact; use of cells which have been thoroughly washed free of surface plasma; and heat inactivation of serum so as to avoid false agglutination from mixed erythrocyte clumping.[19] These and other factors are now fairly well standardized.

At the Eighth International Congress of Hematology held recently, two groups of immunohematologists, using totally different study methods, reported almost the same incidence of platelet antibodies in idiopathic thrombocytopenic purpura and leukocyte antibodies in idiopathic neutropenia.[18, 20]

The principal area of disagreement which still remains concerns the origin of the proteins which give rise to antiplatelet or antileukocyte tests. Are they true antibodies? If so, are they iso-immune or auto-immune in origin? Their nature has been extensively studied by the author and his associates, who found that they are proteins with either agglutinative or lytic properties. They require complement for activity. They can be adsorbed by their selective cellular antigens. Finally, both by chemical and physical analysis, they are gamma globulins in the case of the antiplatelet factor, and either gamma or beta globulins in the case of the antileukocyte factors.[21] It is of interest that during these studies[22, 23] a totally separate glycoprotein was found in normal plasma and serum, which had profound agglutinative and cytotoxic properties when exposed to washed leukocytes and platelets. The physiologic action of this latter material appeared to be inhibited by albumin and hence was only demonstrable after separation of the prealbumin proteins from whole serum.[24, 25] It would appear that this trace component of normal plasma and serum has not led to clinical confusion except in patients with hypoalbuminemia, where a false-positive antibody test might occur. The specific anticellular substance recoverable in the gamma and beta globulins, on the other hand, could only be found in abnormal sera and had the generally accepted properties of true antibodies.

Immunologists point out, however, that even if one agrees they are antibodies, an auto-immune origin has not been proved as conclusively for these blood cell antibodies as for other antibodies, such as the antithyroid antibodies reported by Witebsky et al.[26] Such conservatism is well founded, especially in the case of the leuko-agglutinins where most of the auto-immune concept is founded on evidence which is inferential rather than direct. This concept has been summarized as follows in a recent monograph by Walford:[27]

1. Leukocyte antibodies are statistically associated with neutropenia in a high percentage of cases.

2. In some clinical cases the treatment of the underlying disorder ameliorates the leukopenia and causes the simultaneous disappearance of the positive antibody test.

3. Leukocyte antibodies have been found in the absence of a history of transfusion or pregnancy.

4. Leukocyte antibodies often appear concomitantly with proved erythrocyte or platelet auto-antibodies.

Admittedly only rarely have any workers in the field been able to show the "auto" characteristic of the leukocyte and platelet antibodies against the patient's own cells during a later recovery phase. Nevertheless, a critical review of the present status of this field suggests that although many of the leukocyte and platelet antibodies are "iso" in nature, antibodies also arise in the absence of any known mechanism of iso-immunization and are presumably auto-immune in type. Certainly from the standpoint of the practicing physician these questions are more of academic than practical importance, for application of broad immunologic concepts to certain leukopenic and thrombocytopenic states has improved significantly the diagnosis, management, and understanding of the underlying disease.

TABLE 1

Platelet Antibody Test

	Incubation Time		
	0	45′	90′
Average Normal Serum			
In vitro platelet count	628,000	624,000	620,000
Per cent change in count		−1%	−2%
	(< −5% at 45′ −8% at 90′)		
Average Abnormal Serum			
In vitro platelet count	626,000	520,000	452,000
Per cent change in count		−18%	−28%
	(> −6% at 45′ −10% at 90′)		

METHODS

The data in this report were obtained solely with the author's methods.[16, 17] These technics were selected in order accurately to compare the results with data compiled by others using the same methods, and also because of their relative simplicity and reproducibility. Details of the methods have been published and will not be referred to here. In the case of the platelet antibody test the important features are: (1) the use of serum rather than plasma so as to avoid an anticoagulant factor; (2) the inactivation and decalcification of the serum with a specially-developed barium sulfate, carboxylate resin in order to remove all coagulation proteins with which the platelets normally interact; (3) the use of washed,[28] preserved platelets,[29] which can serve as standard antigen for as long as two years after preparation; and (4) the quantitation of the result in terms of actual decrease in platelet count in the incubation mixture secondary either to agglutination or lysis. The unique features of the leukocyte antibody test are heat inactivation of the serum, addition of human complement, and the

simultaneous screening for all types of antileukocytic antibodies by quantitative measurement of decrease in numbers of motile, nonclumped leukocytes in the test mixture. Results of the platelet test (Table 1) are reported in terms of per cent decrease in discrete, intact platelets after 45 minutes' and 90 minutes' incubation of group specific platelets in the test serum in the presence of added complement. A positive serum will result in a greater than 6% fall in count after 45 min. and in a greater than 10% fall after 90 min., the averages being 18% and 28%. By contrast, a control test utilizing normal serum always shows less than 5% and 8% decrease at the two time increments and in over a thousand assays has averaged only 1% and 2%, respectively. The leukocyte antibody test (Table 2), which we have named the "leukotoxin test" out of deference to the first coining

TABLE 2
Leukotoxin Test

	Incubation Time		
	0	30′	60′
Average Normal Serum			
In vitro white blood cell count	22,400	23,000	21,900
Per cent change in count		+2	+2
Amoeboid motility count	81%		79%
		(Lysis index: 4)	
Average Abnormal Serum			
In vitro white blood cell count	21,000	16,800	13,300
Per cent change in count		−20	−37
Amoeboid motility count	70		59
		(Lysis index: 407)	

of the word by Doan in 1926, is reported in terms both of decrease in count in the incubation mixture and decrease in numbers of normal, amoeboid cells as seen by phase microscopy. There is essentially no decrease in cell count or amoeboid motility when white cells are incubated in normal serum and tested after 30 and 60 min. at 37° C.; whereas positive sera average 20% and 37% decrease in count and greater than 10% simultaneous decrease in amoeboid motility after the same incubation period. The product of these two changes, an arbitrary figure which we call the lysis index, averages a value of four for normal sera, with a range of 0 to 25, whereas the abnormal sera average 407, with a range of 100 to 2,000. Thus, little or no overlap occurs between the positive results and the normal controls.

RESULTS

The following data were obtained from a study of 2,429 serum samples studied in our laboratory since 1951. Approximately 50% of the samples were examined for platelet antibodies alone, 30% for leukocyte antibodies alone, and 20% for both. The sera were obtained from 1,092 patients.

Approximately half of these patients were seen locally. Sera from the other half were mailed to us for study and only clinical protocols were available for evaluation and classification.

Platelet Antibodies: Three-quarters of all sera which gave a positive platelet antibody test came from patients with one of three common syndromes (Table 3). The most frequent diagnosis was idiopathic thrombocytopenic purpura. An attempt was made rigidly to exclude from this group persons whose thrombocytopenia resulted from other diseases, yet the group may inadvertently have contained persons with undiagnosed lupus

TABLE 3

Thrombocytopenic Sera Positive Antibody Tests—Case Distribution

Idiopathic thrombocytopenic purpura		45%
Hypersplenism		
Secondary to:		
Measles, infectious mononucleosis, and infectious disorders	5%	
L.E., arthritis, and other collagen disorders	4%	
Lymphoma, Hodgkin's disease, and Letterer-Siwe disease	3%	
Primary idiopathic hypersplenism	3%	15%
Drug sensitivity		15%
Neonatal purpura		9%
Myelofibrosis and aplasia		6%
Dysglobulinemia Multiple myeloma Macroglobulinemia Cryoglobulinemia		4%
Congenital hemangioma		3%
Unclassified		2%
Leukemia		1%
		100%

erythematosus. Dameshek and others have commented on the frequency with which lupus erythematosus can arise as cryptogenic purpura. Although none of this group of cases with idiopathic thrombocytopenic purpura is known to have subsequently developed lupus, many of the cases have been lost to follow-up study. The second most common disease giving rise to positive platelet antibody tests was hypersplenism, both primary and secondary types, which together comprised 15% of the positive cases. The secondary group was associated with three principal causes: infectious disease, chiefly measles and mononucleosis; malignant disease, chiefly lymphoma, Hodgkin's disease, and Letterer-Siwe disease; and disorders of connective tissue, chiefly disseminated lupus erythematosus and rheumatoid arthritis.

The next group of cases in which positive sera were commonly found

was that in which there was specific drug sensitivity. This important group, first described by Moeschlin and Wagner [30] in the case of Pyramidon allergy, and by Ackroyd [31] and Bigelow and Desforges [32] in the case of Sedormid, quinidine, and other drugs, will be discussed in detail in connection with the leuko-agglutinins.

The less common diseases associated with immune platelet antibodies comprise about one-quarter of the sera tested (Table 3). The neonatal cases proved to be an important group in which the findings were sometimes due to simple passive transfer of antibodies from a mother with chronic or latent idiopathic thrombocytopenic purpura, and sometimes arose as isoimmune antibodies secondary to blood group incompatibility between mother and fetus. In this they resembled erythroblastosis fetalis, but fortunately only rarely were they severe enough to require therapy. The positive anti-

TABLE 4

Leukopenic Sera with Positive Leukotoxin Tests—Case Distribution

I. Drug Sensitivity		35%
II. Hypersplenism		
Secondary		
Hodgkin's disease and lymphomas	10	
Perisplenitis	9	
Rheumatoid arthritis and L.E.	11	
		30%
Primary		18%
III. Leukemia		
Subacute histiocytic	7	
Unclassified leukemic	8	
		15%
IV. Miscellaneous		2%

body tests usually subsided spontaneously over a period of several weeks postpartum, accompanied by corresponding clinical improvement. This was the only group in which platelet or leukocyte *iso*-antibodies led to significant leukopenia or thrombocytopenia. Although temporary suppression of circulating cells has been reported to follow the transfusion of blood containing potent iso-antibodies, none of the patients whose sera contained platelet antibodies showed thrombocytopenia.

One of the more important findings was the infrequency with which leukemia was associated with immunologic purpura. The common occurrence of thrombocytopenia in association with acute and chronic leukemia apparently reflects some other type of pathophysiologic mechanism. In the rare cases where positive platelet antibody tests were found in nontransfused leukemic patients there was either previous infarction of the spleen or a separate auto-immune disorder, such as acquired hemolytic anemia or autoimmune leukopenia. Indeed, the finding of platelet agglutinins in uncomplicated leukemia was so uncommon (1% in 300 positive sera) as to be suggestive evidence against the diagnosis of aleukemic leukemia in patients with atypical pancytopenia.

Leukocyte Antibodies: The diseases in which leukocyte antibodies were found showed important differences from the immune platelet group (Table 4). They fell into three general classifications: drug sensitivity, primary and secondary hypersplenism, and leukemia. The incidence of the drug-induced cases and of the leukemic cases was greatly increased. The association of immune leukopenia with histiocytic leukemia was especially common and in sharp contrast to the platelet findings. Belding et al.[33] have emphasized the frequency of leukopenia as a presenting feature in the Schilling type of monocytic leukemia. The present data suggest that this feature of the disease may reflect an underlying abnormal globulin production as a feature of the uncontrolled histiocytic proliferation.

The observation that 35% of all leukocyte antibody-containing sera came from cases which appeared to be associated with drug sensitivity was a wholly unexpected finding. This in part may have represented inadvertent

TABLE 5

Drug-Induced Leukopenia and Thrombocytopenia

	Non-immune "Toxic"	Immune Hypersensitivity
Type of drug	Alkylating	Diverse sedatives, tranquilizers, and antibiotics
Type of patient	Any	Allergic
Clinical onset	Slow	Abrupt
History	Negative	Same drug previously
Bone marrow	Aplastic	Hyperplastic (maturation arrest)
Antibody test	Negative	Positive or negative
Antibody test + drug	Negative	Positive
Therapy	Drug withdrawal + supportive	Drug withdrawal, steroids + splenectomy

case selection rather than a true index of the frequency of immunologic drug reaction. Several unusual sera from leukopenic patients were referred for specific in vitro drug screening because of our interest in this problem. However, the 35% represented only those leukopenic cases in whom positive evidence of drug-linked leukocyte antibodies was documented, and was believed due, at least in part, to the alarming contemporary use and abuse of new, potent, and sometimes inadequately tested drugs. Another equally important group of drug-induced leukopenias exists, but these leukopenias are totally different in origin and are not related to immune antibodies. These disorders follow use of drugs with specific bone marrow depressing effects, such as nitrogen mustard. Separation of these two groups is of singular importance because of their different management and prognosis (Table 5). The standard antibody test is always negative in the non-immune drug-induced leukopenia, such as that which occurs after nitrogen mustard, triethylenephosphoramide, and similar alkylating agents. On the other hand, the antibody tests usually are positive in the immune hyper-

TABLE 6

Leukopenia
Drug-Induced Immune Reactions

Patient	Drug	Leukotoxin Test			Result
		30′	60′	Lysis Index	
L. W.	L. W. serum	+2	+3	(6)	Negative
	L. W. serum + chloral hydrate (1:10)	−34	−44	(396)	Positive
	Normal serum + chloral hydrate (1:10)	−3	−2	(4)	Negative
H. S.	H. S. serum	+4	+5	(5)	Negative
	H. S. serum + Abdol	−13	−34	(238)	Positive
	Normal serum + Abdol	+1	+2	(4)	Negative
J. S.	J. S. serum	+1	+1	(2)	Negative
	J. S. serum + Sparine, 0.5 mg.	−11	−14	(98)	Positive
	Normal serum + Sparine, 0.5 mg.	+3	−2	(2)	Negative
J. G.	J. G. serum	−18	−21	(210)	Positive
	J. G. serum + aminopyrine (Cosmin), 1:10	−12	−29	(319)	Positive
	Normal serum + aminopyrine (Cosmin), 1:10	−4	+2	(6)	Negative

sensitivity type of leukopenia and thrombocytopenia, provided the sera is drawn early enough in the course of the disease still to contain traces of the offending drug. If the serum has not been drawn until late in the course of disease or until convalescence, addition of the suspect drug in amounts varying between .0001 and .001 gm./ml. to the in vitro incubation mixture is necessary to bring out a positive test. The abruptness of onset and the hyperplastic bone marrow, often incorrectly referred to as maturation arrest, are two other distinctive features of the immune group. The mechanism is believed to be that of the drug acting as a hapten linking the antigen to the antibody. It was possible to demonstrate the antibody nature of the reaction by absorption of the serum against excess antigen prior to addition of the offending agent. In Table 6 are presented the data on four, characteristic, drug-induced, immune leukopenic cases. The first three, due to chloral hydrate, Abdol, and Sparine, respectively, were negative until the

TABLE 7

Absence Leukocyte Antibody Non-Leukopenic Serum—Patients on Drugs*

Drug and Patient	% Change in Total WBC		% Change in Motility	Lysis Index
	30′	60′		
Sparine (R. Y.)	+1	0	−2	0
Chloral hydrate (M. B.)	+1	0	−3	0
Gold salts (R. H.)	−3	−1	−4	4
Biphetamine (L. W.)	−4	+1	−3	3

* All sera incubated 1 hour at 37° C. in presence of added drug prior to routine test.

specific agents were added. The fourth case was positive in the standard test, but showed increased reaction in the presence of aminopyrine. Control studies of the same drugs added in vitro to normal serum were at all times normal. In addition, patients on these same drugs who were free of cytopenia (Table 7) showed consistently negative antibody tests. In some instances it was possible to show that the immunologic reaction was directed against the carrier rather than the pharmacologically active principle in the compound. Selection of a different preparation of the same drug and demonstration of its nonreactivity in the in vitro antibody test was then followed by its use with impunity. Once a specific material led to an immune response, antibody production against it appeared to continue, and

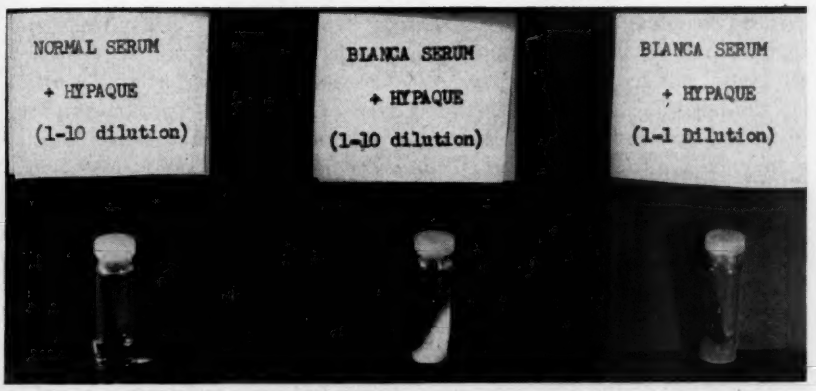


FIG. 1. Gelation and precipitation in serum after addition of Hypaque dye. See text for further explanation.

was demonstrable several years after the last in vivo dose of the drug. Provocative in vivo testing of a drug to which such hypersensitivity exists may lead to serious reaction in the patient. Death due to subsequent thrombocytopenia and intracranial hemorrhage has been reported. Such in vivo testing is difficult to justify now that a safe and relatively simple in vitro test exists.

An additional type of immune drug-induced reaction was observed during these studies: gelation of serum following addition of the offending agent. Figure 1 shows the serum of a diabetic patient admitted to a Boston hospital for evaluation of pyelonephritis. Severe leukopenia and thrombocytopenia developed 48 hours after injection of the 2,4,6-iodinated benzene dye, Hypaque, for intravenous pyelography. The patient had received the same dye six months previously. In studying the patient's plasma for the possible presence of platelet and leukocyte antibodies, the addition of Hypaque resulted in a milky precipitate followed by solid gelation of the serum as noted in the middle tube of the figure. The tube on the left showed

the absence of any reaction upon the addition of the same drug to normal serum. Presumably, the gelation represented interaction of the two antigenic sites of hapten with the high concentration of antibodies in the abnormal serum to form a lattice work, rendering the antibody insoluble. A colleague * suggested that such a system, if it be a true antibody-antigen complex, should be soluble in an excess of the same drug. On the right (Figure 1) may be seen the result of addition of an excess of the same drug. A mild precipitate remained but the gel reaction was prevented.

The precise nature of neither the gel reaction nor the ordinary immune drug reaction is known. The drug may form a hapten linkage between a normal plasma protein acting as an incomplete antigen and the specific antibody, which in turn may be attached to the leukocytes, as postulated

TABLE 8

Drug Sensitivity

(Leukocyte)	(Platelet)
Phenothiazine derivatives	Orinase
Chloral hydrate	Chlortrimeton
Aminopyrine	Gantrisin
Sulfathiazole	Phenacetin
Gold	Coricidin
Decadron	Trinsicon
Apresoline	Biphetamine
Meprobamate	Placidyl
Priscoline	Digitoxin
Librium	Mephyton
Hypaque	
Seconal	
Dilantin	

by Moeschlin; or the drug may attach to the leukocyte and form a complete antigen, which then reacts with an antibody in the plasma. Still a third possibility exists: that the leukopenia is totally separate and merely a nonspecific secondary effect of an antigen-antibody reaction. In the case of the gel phenomenon, one would have to assume either that the latter postulate is correct, or that the serum in question contains enough free intracellular leukocytic protein from lysed cells to permit formation of complete antigen or complete antibody.

In the present study, 23 different drugs were incriminated in one or more cases in the formation of leukocyte or platelet antibodies (Table 8). The drugs are listed roughly in the descending order of the frequency of positive tests. It should be emphasized, however, that this in no way indicates the potential statistical risk of cytopenia from any one of the drugs, since there are no concurrent data on the frequency of use of the different agents. One drug may be prescribed a thousand times more often than another on the same list. The only implications from this table are that the listed drugs *can* produce immune leukopenia or thrombocytopenia (or both, in the case of Dilantin), and that the total incidence of drug sensitivity

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as a cause of immune disorders is probably higher than is generally appreciated. When one considers the probable infrequency with which such cases reach clinical attention and the probably still greater infrequency with which they are seen by an internist or hematologist and subjected to critical study, the magnitude of the present use of hemosensitizing drugs may be appreciated.

Discussion

The evidence presented above deals largely with the association of certain diseases and sera found to contain in vitro evidence of either platelet or leukocyte antibodies. These positive sera were identified during the performance of over 2,000 platelet and leukocyte antibody tests. Although the data show which type of disease occurs most often in a panel of positive sera, they do not indicate the equally important finding of the frequency of positive tests in any single disease. We have not reported the latter, for until very recently such figures have been misleading and of little clinical value. For example, our data for the incidence of platelet antibodies in idiopathic thrombocytopenic purpura (ITP) showed that the finding of a positive test was highly significant and that false-positives were so infrequent as to be negligible. Yet, many patients whose idiopathic thrombocytopenic purpura appeared to be on an immune basis clinically had negative tests both by our technic and that of others. The incidence of positive tests in ITP by our method varied from 65% when the criterion of clinical diagnosis of the disease was used to only 35% when the diagnosis of the disease was restricted to persons with shortened Cr^{51} platelet "survival" as applied by Cohen and Gardner.[34] This raises two questions: (1) Have between one-third and two-thirds of all ITP patients a nonimmunologic basis for their thrombocytopenia? (2) Have the current methods of antibody testing been too insensitive to uncover all of the cases? Present evidence suggests that it is the latter. A recent series of experimental studies suggests that an important "break-through" has been made in improving the sensitivity of our platelet method. Platelets irradiated with two empiric levels of cathode ray, 1×10^6 roentgen equivalent physical and 4×10^6 roentgen equivalent physical, have been used during the past two months as antigen in the standard antibody test. A panel of sera was studied which previously had been found to give negative results, but which derived from cases of clinical purpura that otherwise appeared to fit an immunologic classification. Thus far, 94% of such tests have given positive results with the irradiated platelets, yet with continuing uniformly negative results when tested against normal controls. This degree of irradiation has not led to significant morphologic alteration of the preserved platelets or to decrease in ability of the platelets to show thromboplastic generation, yet it has apparently "opened" the cells sufficiently to permit easier combination of antibody with intracellular antigenic sites. Dausset has postulated that

the antigen with which cellular auto-antibodies interact lies deep within the protoplasm of the cells, whereas the iso-antigens are on the cellular surface and are easily available for agglutination reaction. Such a hypothesis would explain the fact that our methods, using stored cells which may have undergone partial changes in membrane permeability, have been even partially successful in revealing auto-antibodies, whereas all reported methods of macroscopic agglutination reveal chiefly iso-agglutinins. Although data using the sensitized platelets have not been included in the present report, the findings suggest that attempts to record accurately the statistical frequency of a positive antibody test in any single disease should await their broader application.

Prognosis: What prognostic significance can be attached to the presence of a positive leukocyte or platelet antibody test? The follow-up material in this series does not permit tabular reports; however, a few general observations were noted. The most striking of these was the change in antibody titer in the same individual when it was observed over a period of years. In nearly all cases where long-term evaluation was possible, an eventual recurrence of a positive agglutination reaction occurred, even if the antibody test had reverted completely to normal and the patient had entered clinical remission. In general, the titer of circulating antibodies was not as high when the test again became positive, although evidence of continuation of the immune mechanism could be found. The principal exceptions were the cases of neonatal purpura, where further antigenic stimulation and transfer of maternal antibodies ceased immediately postpartum, and the childhood purpuras, especially those secondary to measles and mononucleosis.

In all other cases, the return of anticellular antibodies was so nearly uniform a finding as to suggest that no one is ever "cured" of idiopathic thrombocytopenic purpura, primary neutropenia, or hypersplenism, in the strictest sense of the term. It would appear that once production of autoimmune globulin has begun in clones of new antibody-producing cells as postulated by Dameshek,[35] suppression of the cells by steroids, or removal of one of the major foci of such cells through splenectomy, only decreases the titer sufficient to effect a remission without eliminating the actual cause.

Harrington[36] reports a better clinical response to splenectomy in patients with positive platelet tests than in a comparable group with negative tests. Our data are compatible with this conclusion, but too few cases in our series were splenectomized to give the data statistical validity. On the basis of the very recent work with irradiated platelets, however, it would appear that ITP patients with positive and negative tests differ only in their degree of antibody activity rather than in their fundamental pathophysiologic abnormality.

The presence of leukopenia as a presenting finding in acute leukemia has been reported by Kimura[37] to be of significance in regard to probability of clinical improvement on steroid therapy. He noted that only 5% of all

cases of leukemia with an initial white count above 10,000 responded favorably to steroids, whereas 50% of a group with initial counts below 10,000 improved. Our finding of frequent leuko-agglutinins in the group of aleukemic leukemics suggests that the improvement may result from temporary suppression of this hyperimmune mechanism, without, of course, any change in the course or fatal outcome.

Treatment: The principal conclusion which appeared warranted from determination of the antibody tests concerns general therapeutic management. The presence of circulating platelet antibodies in a case of purpura made obvious the transient nature of any improvement which would follow platelet transfusions, and this was borne out by study. Temporary control of antibody production, on the other hand, appeared helpful and, in some cases, life-saving. This was accomplished by the liberal use of prednisone and its analogs. In cases where serious relapse occurred and steroids were contraindicated, splenectomy was useful.

The use of antibody tests in drug-induced immune purpura and agranulocytosis was of unique therapeutic value. Not only did such tests indicate which drug (or drugs) was the offending agent, so that future use could be interdicted, but in some instances they made specific therapy possible as in the case of British antilewisite and ethylenediaminetetra-acetic acid for heavy metal intoxication with gold. Complexing the free circulating metal by such chelating agents led to prompt reversal of the clinical illness. In occasional cases in the drug-induced group, the disease appeared to continue after cessation of the offending agent. These cases were managed by routine steroid therapy or splenectomy.

The findings of positive leukocyte or platelet antibody tests in Hodgkin's disease, although uncommon, proved therapeutically important. Management of the immune hematologic findings as an independent problem, prior to institution of specific lymphoma therapy, generally improved the patient's condition and permitted the more liberal use of radiation and alkylating agents.

Summary and Conclusions

Simple in vitro tests now exist for the determination of antiplatelet and antileukocyte antibodies. These tests are of help in the diagnosis and management of diverse hematologic disorders associated with immune mechanisms. The principal diseases from which sera containing platelet auto-antibodies could be isolated were idiopathic thrombocytopenic purpura, hypersplenism (both primary and secondary), drug sensitivity, and neonatal purpura. Platelet antibodies were notably uncommon in acute and chronic leukemia. The principal diseases in which sera containing antileukocyte antibodies existed were hyperimmune drug sensitivity, hypersplenism (both secondary and primary), and aleukemic leukemia. The incidence of drug-mediated leukocyte antibodies was unexpectedly high.

This was believed due both to inadvertent case selection in the series and the widespread use of potent new therapeutic agents. The frequency with which white cell or platelet antibodies occurred in any one of the above disorders was not determined from these data. It is believed that current improvement in methodology will lead to data on statistical frequency which may largely supplant previous reports.

The principal clinical benefits of use of the platelet and leukocyte antibody tests are discussed in terms of prognosis and treatment.

SUMMARIO IN INTERLINGUA

In le curso de 10 annos, 2.429 specimens de sero esseva studiate pro anticorpore anti plachettas e leucocytos. Le quantitative micro-tests del autor esseva usate pro deteger auto-anticorpore. Le datos esseva usate pro analysar le incidentia de immunologicamente inducite leucopenia. Le signification de positive tests in prognose e therapia esseva etiam evalutate.

Tres quartos del seros que monstrava un positive test de anticorpore anti plachettas veniva ab patientes con un de tres syndromes commun: Purpura thrombocytopenic idiopathic, hypersplenismo (primari e secundari), e sensibilitate pro drogas. Minus commun morbos associate con immunologicamente inducite thrombocytopenia esseva purpura neonatal, myelofibrosis, dysglobulinemia, e hemangioma congenite.

Le casos clinic in que anticorpore anti leucocytos esseva trovate communmente monstrava importante differentias. Le causa le plus commun de leucopenia immunologic pareva esser sensibilitate pro drogas. Iste categoria representava 35% del casos. Hypersplenismo habeva le secunde rango, specialmente le forma secundari a disordines de collageno e a lymphoma. Leucemia aleucemic esseva etiam associate frequentemente con leuco-agglutininas, durante que anticorpore anti plachettas esseva trovate rarmente in casos de non-complicate leucemia.

Le signification de positive tests de agglutination de leucocytos e de plachettas esseva etiam evalutate. Depression del formation de anticorpore esseva usualmente effectuabile per medio de corticosteroides, sed in certe casos etiam splenectomia esseva necessari. In casos de immun purpura e leucopenia a induction drogal, le uso de tests in vitro rendeva possibile le diagnose specific del droga particular que habeva causate de disordine clinic, sin le necessitate de utilisar le riscose tests in vivo pro sensibilitate drogal.

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POST-STEROID PANNICULITIS *

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THE great majority of untoward effects of steroid therapy follow one of two general patterns. Some of them, such as sodium retention, osteoporosis, and decreased resistance to infections, are attributable directly to the hormones and not to the diseases for which the steroids are administered. They appear *during* the course of therapy and subside afterwards. Others consist of exacerbations of the underlying disease, are occasionally more severe than the initial manifestations, and occur *after* discontinuation of the hormones.

Recent reports [1-3] have described a new and apparently rare syndrome which appears to be a complication of steroid therapy, particularly of prednisone administration, but which differs fundamentally from all others. It is characterized by a nodular, tender, itching panniculitis which sometimes appears after therapy has been stopped, as do complications following the second pattern described above; but, unlike them, it does not consist of an exacerbation of features of the underlying disease. Nodular panniculitis thus resembles the first type of undesirable effects, such as osteoporosis and sodium retention, except that it occurs *after* rather than *during* treatment. This relationship to the apparent causal agent is peculiar and has few parallels in clinical medicine.

Four additional cases clinically resembling those previously described [2] have been observed by the authors over a two-year period. They were milder, and occurred after less massive steroid administration, compared with the original cases. Each of two patients had a clinical rebound and a nodular panniculitis after the same course of prednisone therapy, but at different times, thus graphically illustrating the nonidentity of these two post-treatment complications. Because of these distinctive features, and because of the intriguing nature of this little-known disorder, these four new cases are reported.

CASE REPORTS

Case 1: P. S., a 7-year-old white boy, was admitted to Irvington House on July 9, 1958. Two months before, because of joint pains, he had been admitted to another hospital, where systolic and diastolic apical murmurs were first heard. Erythrocyte sedimentation rate was 28 mm./hr., the C-reactive protein test was 2-plus, and the

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antistreptolysin O titer was 333 U./ml. A chest x-ray showed slight cardiomegaly. Prednisone, 40 mg. per day, was started on May 7, with prompt clinical and laboratory response. Twenty days later gradual withdrawal of prednisone was begun. During this period the patient was transferred to Irvington House for further care. On July 24 the steroid administration was discontinued, and for the next three days ACTH, 25 mg. per day, was given. Concomitant with the steroid therapy, aspirin was also given (Figure 1).

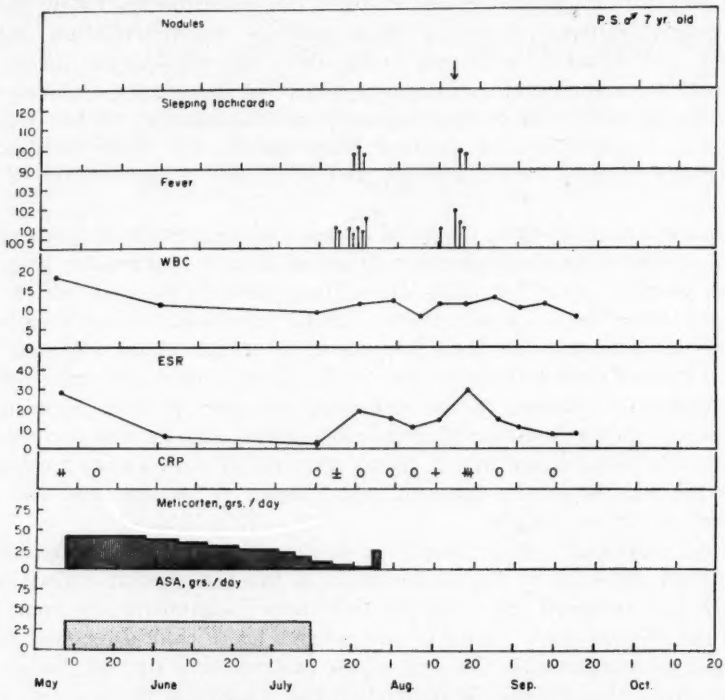


FIG. 1. Clinical and laboratory features of case 1.

During the withdrawal of prednisone the patient had a low-grade fever, sleeping tachycardia, a positive C-reactive protein test and an increase in the erythrocyte sedimentation rate. Both the clinical and the laboratory features of this episode, which probably constituted a rheumatic rebound or "escape," subsided spontaneously within a week.

On August 15, 18 days after the discontinuation of therapy, a round, red area about 6 cm. in diameter was noted on the left buttock. It was pruritic, indurated, and tender. No injections had ever been given in that area and there was no evidence of perifollicular inflammation. Fever and sleeping tachycardia reappeared, with an increase in the erythrocyte sedimentation rate and a positive C-reactive protein test. Two days later the local inflammatory signs were markedly reduced and after three more days were gone, leaving behind only a slight pigmentation of the skin. The skin was not atrophied or dimpled, nor did such signs appear during the next two months. The patient has been followed for 20 months and has remained in apparent good health.

Comment: This patient had an episode of nodular panniculitis after receiving a total of 2,050 mg. of prednisone. The panniculitis occurred 20 days after the end of prednisone treatment and 18 days after a final four-day course of ACTH. It was distinctly separate from what appeared to be a rheumatic rebound, which had subsided spontaneously two weeks before. The course of the panniculitis was mild and short, despite its conspicuous initial signs.

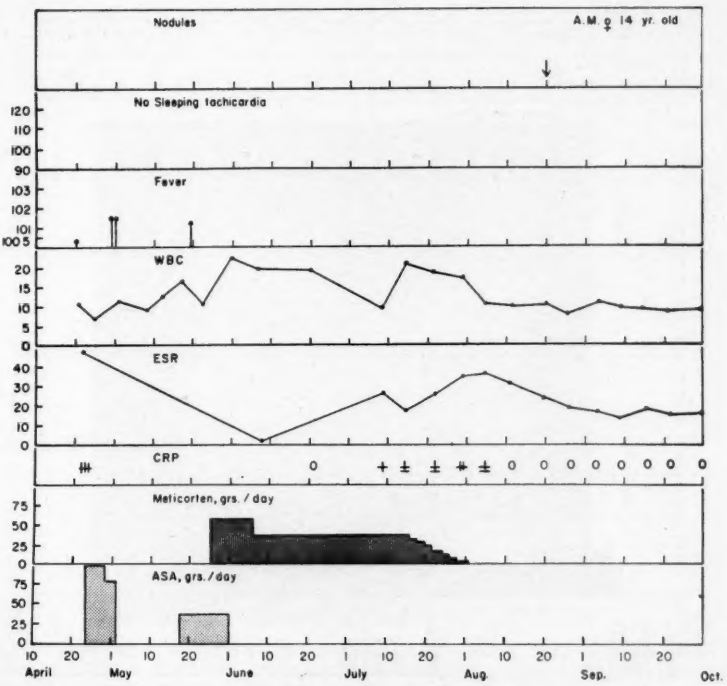


FIG. 2. Clinical and laboratory features of case 2.

Case 2: A. M., a 14-year-old Puerto Rican girl, was admitted to Irvington House on July 3, 1957, while receiving steroid treatment for her first attack of rheumatic fever. At the beginning of the preceding April she had had fever and arthritis of both knees. Ten days after the onset of symptoms she was admitted to another hospital, where a grade III apical systolic murmur was heard. The antistreptolysin O titer was 1,250 U./ml., the ESR was 54 mm./hr., the CRP test was 3-plus. Aspirin was started but was discontinued after eight days because of toxic symptoms (Figure 2). Following discontinuation of the drug she again had fever and arthralgia of both knees. Aspirin was resumed at a lower dosage, and prednisone was added to the treatment on May 24. Clinical and laboratory signs of rheumatic activity then subsided within a few days. While on steroid therapy the patient developed severe diffuse acne, cushingoid facies, and abdominal striae. During the withdrawal of the drug, abnormalities of the acute phase reactants reappeared and

then disappeared spontaneously. This episode, which most likely represented a mild rheumatic rebound, had almost completely subsided by August 20, when a 4 by 4 cm. area, erythematous, indurated, pruritic, and tender, was noted in the right popliteal region. Four days later the nodule had all but vanished, leaving behind only a slight pigmentation of the skin.

Comment: A clinically typical episode of nodular panniculitis occurred in this patient after a total of 2,640 mg. of prednisone. Its manifestations were mild and subsided spontaneously within four days. The onset of

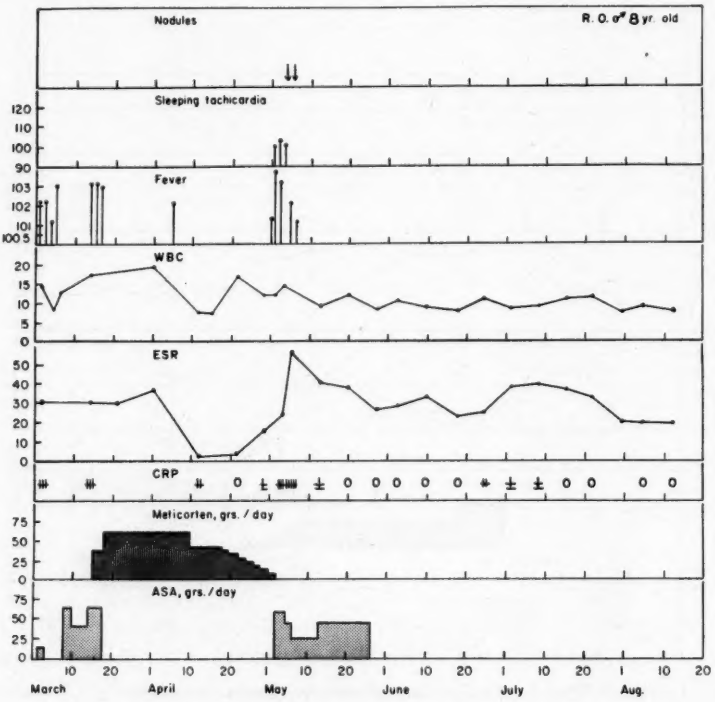


FIG. 3. Clinical and laboratory features of case 3.

symptoms occurred 20 days after discontinuation of the drug and while the manifestations of a mild (or "laboratory") rheumatic rebound, which had preceded the panniculitis, were disappearing.

Case 3: R. O., an 8-year-old Puerto Rican boy, was admitted to Irvington House on April 12, 1957, because of a second attack of rheumatic fever complicated by pneumonia. On March 1 he had developed fever and arthralgia of the left foot. On admission, systolic and diastolic murmurs were heard at the apex, the liver was palpable two fingerbreadths below the right costal margin, and the breath sounds were found to be diminished over the base of the left lung. An x-ray of the chest showed slight cardiomegaly and an infiltrate in the right lower lobe of the lung.

The ASO titer was 1,200 U./ml., the ESR was 32 mm./hr., the CRP test was 3-plus. Shortly after admission he developed arthritis of the right wrist. Initial treatment consisted of administration of aspirin and parenteral penicillin. Twelve days after onset of symptoms the patient developed a pericardial friction rub, further cardiac enlargement, and subcutaneous nodules on the left elbow and wrist. The latter were nontender, the skin was freely movable above them, and they showed no signs of inflammation; they were considered, therefore, to be typical rheumatic nodules. Prednisone was started at this time (Figure 3), and during the next two weeks the nodules and the friction rub disappeared. While on prednisone the patient developed mumps. On April 18 gradual withdrawal of prednisone was begun and on May 2, as prednisone was stopped, the patient again developed arthritis of the right wrist, with fever, sleeping tachycardia, and abnormal acute phase reactants. On the same



FIG. 4. Appearance of the face of case 3 four days after discontinuation of prednisone therapy. Notice the shiny center and dark periphery of the lesion on the cheek, and the small dark area in front of the ear.

day aspirin therapy was reinstituted. Two days later a diffusely indurated, shiny area, 2 by 3 cm., was noticed on the left cheek. Similar lesions appeared two days later on the right cheek and in front of the left ear (Figure 4). The latter nodules disappeared shortly thereafter. The nodule over the left cheek became gradually smaller and was barely palpable 10 days after its appearance. The overlying skin then acquired a bluish discoloration. None of the nodules was ever itchy or tender. There was no atrophy of the skin or depressed scars at the site of the lesions, nor did they develop during the subsequent year of observation.

Comment: In this patient a clinical picture of post-steroid nodular panniculitis occurred after a total of 2,025 mg. of prednisone, two days after the end of therapy, and its appearance was not prevented by aspirin administration. The panniculitis was practically concomitant with a definite clinical rheumatic rebound with arthritis.

Case 4: R. B., a 12-year-old Negro boy, was transferred to Irvington House on February 4, 1959, for continuation of treatment of his first attack of rheumatic fever with carditis. The preceding December 2 he had been admitted to another hospital because of fever and a "cold" of two days' duration. Tachycardia and systolic and diastolic murmurs at the apex were present. The ASO titer was 2,500 U./ml., the CRP test was 3-plus, the ESR was 60 mm./hr.

Prednisone administration was started on the day of admission to the other hospital in a dosage of 80 mg./day, which was reduced to 60 mg. two days later. For the first two days aspirin was also given. The prednisone was tapered at the rate of 10

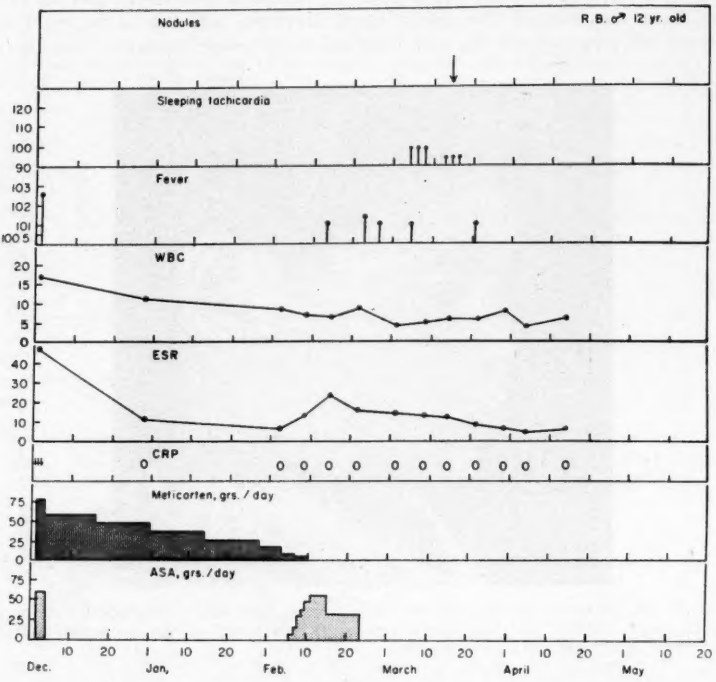


FIG. 5. Clinical and laboratory features of case 4.

mg. every two weeks until January 28, and at a faster rate thereafter until discontinuation on February 10, 1959 (Figure 5). Aspirin was added to steroid treatment from February 6 through February 24. The diastolic apical murmur disappeared, while the systolic murmur persisted and was considered to be indicative of mitral regurgitation.

Following discontinuation of therapy the patient had a slight increase in the ESR with isolated spikes of temperature up to 101°F. These abnormalities subsided spontaneously. On March 15 the patient complained of pruritus in the left forearm. The following day, a red, swollen, indurated, slightly tender area, 3 by 3 cm., appeared in that region. Within the next three days the inflammatory changes decreased markedly, the itching disappeared, and only a nontender, movable, superficial nodule the size of a dime could be palpated.

A biopsy of the nodule was performed five days after its appearance. Histologi-

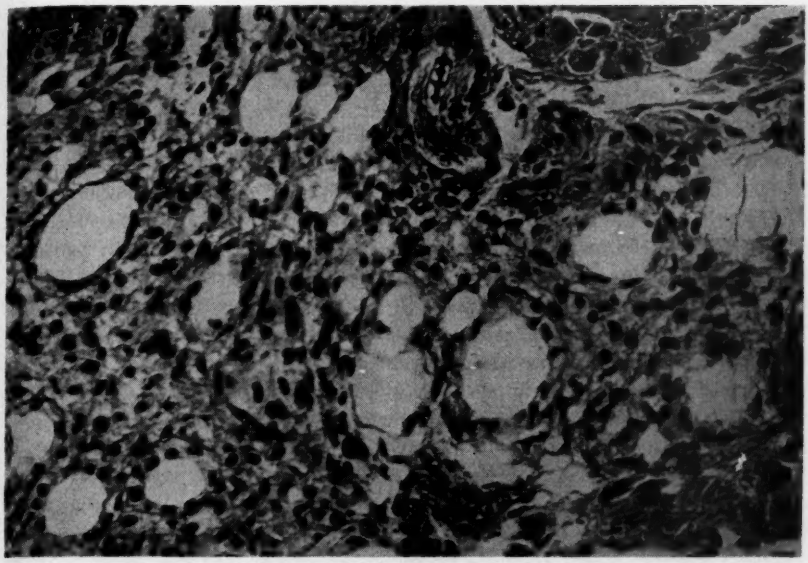


FIG. 6. High power view of a histologic section of a subcutaneous nodule in case 4. Hematoxylin and eosin stain. Numerous inflammatory cells (histiocytes, lymphocytes, occasional polymorphonuclear leukocytes, and plasma cells) infiltrate the interstices between the few residual adipose cells.

cally, the nodule consisted of fibroadipose tissue, with mild to moderate infiltration of lymphocytes, histiocytes, and occasional plasma cells (Figure 6).

Comment: This patient had an episode of nodular panniculitis after a total dose of 2,765 mg. of prednisone, 35 days after discontinuation of the drug. The panniculitis was not accompanied by abnormalities of the acute phase reactants, and it followed the spontaneous subsidence of a mild clinical rheumatic rebound. The clinical manifestations were mild and could have

TABLE 1

Clinical and Laboratory Manifestations of Four Cases of Post-steroid Panniculitis

	Case 1	Case 2	Case 3	Case 4
Pruritus	+	+	—	+
Tenderness	+	+	—	+
Erythema	+	+	+	+
Fever	+	—	+	+
Skin pigmentation	+	+	+	—
Location	Buttock	Leg	Cheeks	Arm
ESR	+	—	+	—
CRP	+	—	+	—
WBC	+	—	+	—
Prednisone received (mg.)	2,050	2,640	2,025	2,765

been easily overlooked; the histologic findings were fundamentally similar to those previously reported.[2]

Conclusions

Table 1 summarizes the main clinical and laboratory features of the four cases described. Erythema was present in all patients; pruritus, fever, tenderness, and residual skin pigmentation were the most common associated features. Erythrocyte sedimentation rate, white blood cell count, and C-reactive protein test were abnormal in two of the four cases: in one they appeared to be unrelated to the underlying rheumatic process which had already flared up and had subsided by the time the panniculitis appeared; in the other, however, the panniculitis was concomitant with a rheumatic rebound and therefore the latter might have been the sole cause of the abnormal acute phase reactants. The distribution of the nodules involved the extremities (flexor region), the cheeks, and the trunk. The total doses of prednisone received were in all cases above 2,000 mg., but consistently below those reported in previous cases.[1, 2]

These observations confirm the finding that nodular panniculitis is a syndrome which can be differentiated clinically from rheumatic nodules, Weber-Christian syndrome, and erythema nodosum. The differential diagnosis with rheumatic nodules is clear cut, since the latter are not accompanied by pruritus, tenderness, or erythema, usually appear over bony surfaces, and heal without residual pigmentation of the overlying skin. None of our patients had the skin atrophy, the depressed scars, or the spontaneously relapsing course which are characteristics of the Weber-Christian syndrome. Erythema nodosum is characteristically distributed over the extensor surfaces of the limbs and is not pruritic. In addition, the etiology of the last two syndromes is obscure, and that of rheumatic fever is streptococcal, whereas the etiology of the nodular panniculitis described appears to be related, however complex and indirect the relationship might be, to the previous administration of prednisone.

Nodular panniculitis can be classified as a post-treatment complication of prednisone administration. Because of this time relationship with therapy, and because the majority of episodes of nodular panniculitis thus far reported have occurred in rheumatic patients, it might be tempting to consider the syndrome as a manifestation of rheumatic "rebound." The clinical and histologic characteristics of nodular panniculitis, however, differ sharply from those of rheumatic nodules—the rheumatic manifestation most akin to nodular panniculitis.[2] Moreover, an analysis of the present cases reveals that in three patients nodular panniculitis occurred after the signs of the previous rheumatic rebound had spontaneously subsided and more than two weeks after discontinuation of prednisone therapy. Rheumatic rebounds seldom reappear after having spontaneously subsided, and only rarely follow cessation of treatment by periods as long as two weeks.[4]

The mechanism by which prednisone might cause the adipose cellular damage which reveals itself clinically as nodular panniculitis can only be a matter of speculation at this stage. Unlike most pathologic processes, nodular panniculitis follows its apparent causal agent, administration of prednisone, only after the latter has been withdrawn. Indeed, the manifestations of panniculitis seem to be relieved, paradoxically, by the resumed administration of the very causal agent.[2] From this general standpoint the relationship between prednisone and nodular panniculitis resembles that between alcohol and delerium tremens in alcoholics, and between narcotic agents and withdrawal symptoms in drug addicts. The possibility that nodular panniculitis is a manifestation of the temporary adrenal insufficiency which may follow steroid administration is intriguing but unlikely, since this syndrome does not seem to have been described in Addison's disease, and since the interval between termination of prednisone therapy and appearance of panniculitis is longer than one would expect in a simple, direct, post-therapeutic hypoadrenalism.

In the field of more specific pathogenetic mechanisms, it may be no mere coincidence that one of the side effects of prednisone administration is the accumulation of fat in the subcutaneous tissue, that many of the affected children have spectacular gains in fat,[2] and that many lesions are localized in areas of particularly striking fat accumulation, such as the cheeks of patients with "moon facies."[2] The loss of the factor leading to the accumulation of fat and the attendant accelerated fat removal might, conceivably, injure the adipose cells. Whether this is a satisfactory pathogenic theory of nodular panniculitis, however, remains to be determined by further observation and by experimentation.

Summario in Interlingua

Un syndrome characterisate per panniculitis nodular, hyperesthetic, e pruriente esseva recentemente describite como occurrente post un therapia massive de prednisona pro febre rheumatic. In le presente reporto quatro casos additional de iste apparentemente infrequente syndrome es describite.

Le episodios hic reportate esseva minus sever que illos del reporto original e occurreva post minus massive administrationes de prednisona. In tres del casos, le lesiones lassava un area pigmentate in le pelle. Un deprimite cicatrice non esseva producite, como il haberea essite le caso in le syndrome de Weber-Christian. Le lesiones non afficeva le superficies extensori del extremitates, como il haberea essite le caso in erythema nodose. Un photographia del lesiones in un del patientes es reproducite, e le apparentia histologic de un lesion in un del altere patientes es presentate.

Le characteristicas clinic e histologic de iste syndrome ha previemente su differentiation ab resaltos rheumatic. Iste differentiation es rendite plus evidente per le observation in duo del casos hic reportate del presentia de un clinic resalto rheumatic e un panniculitis post steroide, occurrente a differente tempores post le cessation del medication.

Le syndrome de panniculitis post steroide ha un relation peculiar con su apparente agente causal, le administration de prednisona. Per contrasto con le majoritate del

complicationes de therapia a steroide, illo occurre post e non durante le administration del droga. Analogias a base de iste characteristica fundamental es presentate. Un theoria pathogenetic es proponite.

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ERRATUM

In the paper "A Local Outbreak of Trichinosis" by Shields, Smith, Cook, Witte, and Lindsey, which appeared in Volume 54, No. 4 (April, 1961), page 742, line 26 should read: "Garbage should be cooked at 212° F. for 30 minutes in order to kill *Trichinella* larvae before it is fed to hogs."

PREVENTIVE MEDICAL MASS RECONDITIONING ABROAD—WHY NOT IN U.S.A.?*†

By W. RAAB, M.D., F.A.C.P., *Burlington, Vermont*

MODERN man in the increasingly industrialized, denaturalized Western world is deteriorating physically and spiritually. Neuroses, gastrointestinal and metabolic disturbances, incapacitating conditions of the muscular system, and, most ominous of all, insidiously developing cardiovascular degenerative changes of neurovegetative and dietary origin constitute the bulk of the rampant "diseases of civilization and prosperity." They may be attributed specifically to these factors: lack of physical exercise; derangements of the daily rhythm (night shifts); monotony of assembly line work; unfavorable working postures; noises; imbalanced dietary habits; socioeconomic pressures, tensions, anxieties, and frustrations; and to prosperity-induced sophistication, spiritual aimlessness, and boredom.

In the United States, heart diseases lead all causes of death with 55% (Figure 1),[1] and an estimated two and one-half billion dollars in earnings are lost annually[2] through heart disease alone. About 30% of disability payments under the Social Security laws are paid to those having circulatory diseases.[2a] In prosperous West Germany, cardiovascular deaths account for 40% of all deaths and one-third of the working population becomes invalid, on the average, 10 years before reaching the standard retirement age of 65, chiefly due to diseases of civilization.

In the area of rehabilitation of the overtly sick and incapacitated, a large amount of outstanding pioneering work has been initiated and is being carried out in the United States to restore the earning power of those afflicted by fully developed pathologic conditions. On the other hand, no attempts at organized mass prevention (except for infectious diseases and specific industrial hazards) have yet been undertaken in this country. It seems that, until quite recently, the dramatic triumphs of modern curative medicine and the remarkable achievements of late rehabilitation have fascinated the professional medical and public mind; conversely, there is virtually no interest in the unglamorous proverbial "ounce of prevention."

In sharp contrast to the total lack of organized preventive measures for "health protection" against the hazards of supercivilized living in the United States, social security insurance organizations and big industries in West Germany, Switzerland, Austria, and the Soviet Union, have for years applied successful policies of large scale prophylactic mass reconditioning

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for the benefit of workers, employees, and executives whose health appears to be endangered by their living and working conditions. The government of East Germany started an ambitious "seven-year plan" in 1959 for the same purpose.

The so-called "Ohlstädter Kur," initiated in 1953 by Beckman [3] in the Bavarian mountains, has been accepted with some modifications as a model procedure for reconditioning practices in 14 other German reconditioning centers.

Ten such centers were visited by this writer in the fall of 1960. The following report is based on personal conversations with the medical staffs

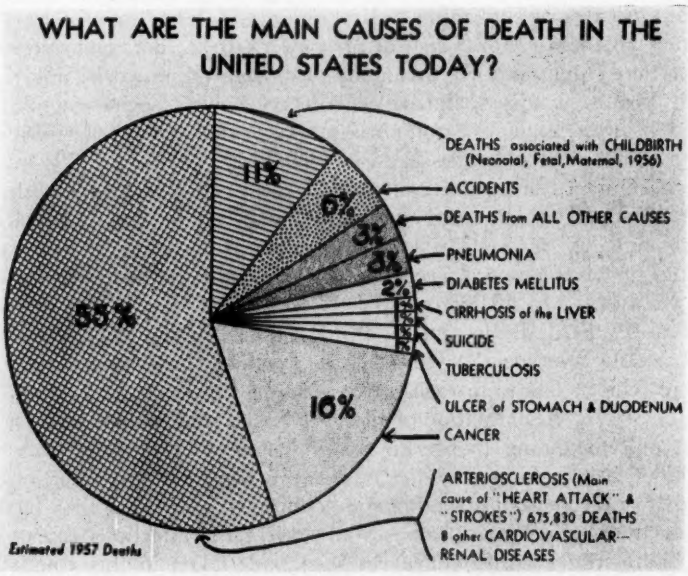


FIG. 1. Reproduced from "International Health Study" of the U. S. Senate Committee on Government Operations. (Courtesy the Hon. H. H. Humphrey, Subcommittee Chairman.)

of these centers, with directors of sponsoring insurance organizations and industrial social service departments (Opel Automobile Works, Siemens Halske Electrical Works, Mannesmann Pipe Casting Industry), with insurance lawyers, and with referring insurance physicians. In addition, a considerable amount of literature on the subject of health preservation measures and of their legislative regulations abroad has been assembled.

West German Reconditioning Centers and Programs: The fundamental principle which all of the West German reconditioning policies have in common is a temporary complete replacement of the "prepatient's" customary living habits by his full participation in a systematic program of vigorous

physical activity in close contact with an appealing and soothing natural environment. These are the salient features:

1. Admission for four to six weeks to one of the reconditioning centers ("Kurheime") located in the most attractive and most climatically suitable areas of the German countryside, such as the Bavarian Alps, Black Forest, Rhineland, and the beaches on the shore of the North Sea.



FIG. 2. **Group hiking in training suits in the Black Forest near the reconditioning center Badenweiler of the District Insurance Organization, Baden.** (Courtesy Dr. W. Groh.)

2. Participation in medically supervised all-year programs of graded, increasingly strenuous outdoor group exercises (20 to 25 persons), virtually without regard to weather conditions. The daily routine consists of calisthenics, breathing exercises, extensive hiking, mountain climbing ("Terrain-Kuren"), swimming, skiing, outdoor games (without any attempt at competitiveness or drill), alternating with periods of complete relaxation (Figures 2, 3). Hydrotherapy (according to the time honored

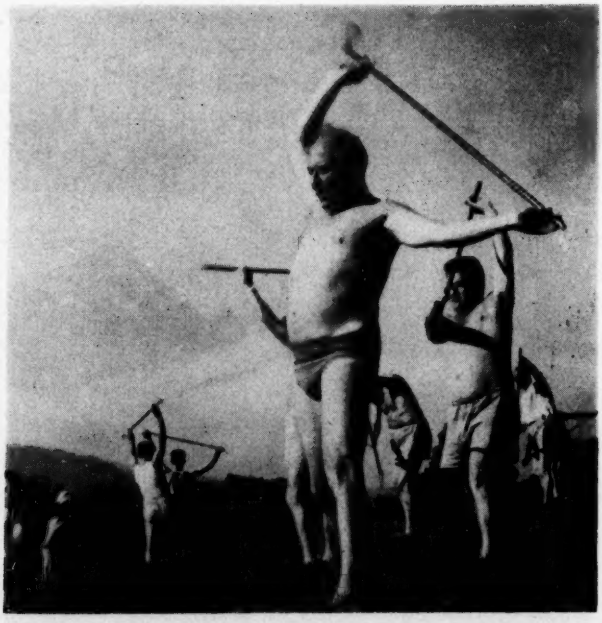


FIG. 3. Outdoor exercises at the "Anstalt für Gesundheitssicherung und Uebungsbehandlung" of the District Insurance Organization Unterfranken, Ohlstadt, Upper Bavaria. (Courtesy Dr. P. Beckmann.)

methods of Priessnitz and Kneipp), wading through brooks, running barefoot on meadows, mud baths, underwater massage, skin stimulation through dry body brushing, and Finnish sauna baths also occupy a prominent place (Table 1).[4] The diet contains relatively small quantities of fats and salt

TABLE 1

Weekly Distribution of Reconditioning Activities at Castle Schönberg Reconditioning Center*

Activity	No. Days	Period	Total
Calisthenics, breathing exercises, massage, brushing, early morning running on meadows	6	¾ hr.	4½ hrs.
Sports	2	1½ hrs.	3 hrs.
Hiking in groups			9 hrs.
Baths, water applications	3	20 min.	1 hr.
Sauna baths			2 hrs.
Relaxation practice	3	1 hr.	3 hrs.
Lectures on health problems	3	40 min.	2 hrs.
Handcraft	2	2 hrs.	4 hrs.
Evening entertainment			3½ hrs.
Weekly total			32 hrs.

* After Schauwecker.[4]

but plenty of vegetables and fresh fruit. Light alcoholic beverages are allowed in moderation. Smoking is not permitted on the premises. Individual psychosocial interviews are given by the resident physicians when they are indicated.

3. Evenings are largely devoted to lectures and discussions on health problems, illustrated by slides and movies. Television is limited to a few selected programs. Private radios are barred.

4. On two free afternoons and during the weekend, voluntary participation in cultural activities is encouraged; handicraft, chamber music, theatrical performances, guided excursions to nearby historic sites and art monuments are typical pursuits.

5. All prospective trainees are admitted with a written report from the referring insurance physician. During the first two or three days at the center, they undergo another thorough medical examination. A report on this and on a subsequent concluding examination is forwarded to the admitting organization upon discharge of the trainee. The latter receives instructions and pamphlets concerning continued home exercises and other measures. Four to 14 free days for reacclimatization at home are allowed in many cases after the period in the reconditioning center. In some instances, a systematic follow-up concerning subjective conditions, work performance, and continued home exercising is attempted by means of questionnaires distributed periodically. If necessary, trainees are readmitted to the centers at about two-year intervals. Those who refuse full cooperation in the programs without medical justification are expelled.

Federal Law Concerning Reconditioning: After the reconditioning procedures outlined above had proved to be successful over a period of four years in a growing number of centers under the voluntary sponsorship of several social insurance organizations, a federal law (§ 1236 RVO) was passed in 1957 by the German Bundestag. It reads in part: "In case the earning capacity of an insured person is endangered or diminished due to illness or other impairments or weakening of his or her physical or mental forces, and if it can foreseeably be maintained, substantially improved, or restored, the sponsor of the workers' social security agency (the federal insurance agency for employees) is empowered to grant measures . . . for the maintenance, improvement or restoration of earning capacity."[5] Emphasis on the words "endangered" and "maintenance" permits a remarkably liberal policy of admission to the reconditioning centers. Rejected applicants are entitled to apply to the social courts for re-evaluation of the decision made by their insurance organizations.

Financing of the Reconditioning Centers: Approximately 15,000 persons are admitted annually to the German reconditioning centers (including cases of "rehabilitation" in which manifest disease has already caused a temporarily complete loss of earning capacity). With the exception of two insurance organizations which deduct one or two weeks from the trainee's

regular four-week vacation period as partial compensation, all other sponsoring agencies cover the entire cost of his stay at a reconditioning center, including transportation from his home and back to it, all medical services, special treatments, and loaned equipment for personal use, such as training suits, raincoats, bathing trunks, and hiking and climbing shoes. The cost of a four-week reconditioning period per person is estimated as approximately DM (German Mark) 740 to 1,000, equal to $184 to $250. Private trainees are accepted in some centers in small numbers at their own expense.

During the trainee's absence from work (including the subsequent reacclimatization period), his wife receives 55% of his normal net income.

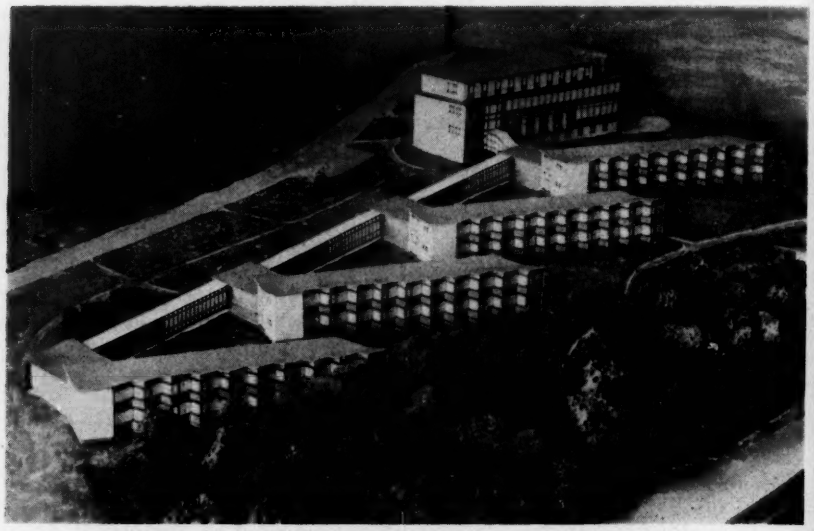


FIG. 4. Model of new reconditioning center at Bad Salzig on the Rhine for 100 members of the District Insurance Organization Rheinpfalz. (In the main building: mess hall, recreation hall, medical staff quarters and offices, laboratories; in the wings with southern exposure: trainees' rooms, gymnastics teachers' quarters, baths.) (Courtesy Dr. Radermacher.)

This is increased 5% each for one to five dependent children, thus reaching a maximum of 80%. In some centers, the trainees receive daily pocket money of DM 1,00, equal to 25 cents. About 30% of the total social insurance costs are borne by the state. Some social security organizations earmark 10% of their revenues for "health preservation."

Physical Plants and Facilities: The physical plants of the 15 German reconditioning centers are of a diversified character. They accommodate from 40 to 120 persons at a time. Ten are occupied exclusively by men, two exclusively by women, and two are mixed. A few consist of groups

of converted peasant farms with a central mess hall, a gymnasium, a bath and medical building; others are housed in former castles, sanatoria, or hotels, and some are established in specially erected large modern buildings with extensive physiotherapeutic facilities, sauna baths, social halls, auditoriums, libraries, and medical laboratories. Three additional new centers are under construction (Figure 4).

Nearly all centers are remotely situated amid forests, and are near lakes, brooks, and waterfalls. Two are located on sandy beaches.

Diagnostic inventory is usually limited to electrocardiograph, x-ray, and the basic laboratory items for urine and blood analysis. Some centers are also equipped for spirometry, ergometry, phonocardiography, and skin thermometry.

TABLE 2

Results from Reconditioning

Clinical Conditions	Number of Cases	Improved*	No Improvement†	Partial Improvement‡
1. Vegetative dystonia with general symptoms	217	177	18	22
2. Vegetative dystonia with cardiac and circulatory symptoms	390	348	21	21
3. Vegetative dystonia with gastrointestinal symptoms	71	54	8	9
4. Hypotonia	78	74	4	—
5. Peripheral circulatory disturbances	46	34	6	6
6. Exhaustion (including conditions after surgery and prolonged illness)	145	127	5	13
7. Chronic bronchitis with and without asthma	82	58	16	8
8. Rheumatic symptoms, spondylarthroses, osteochondroses, arthroses	96	68	12	16
9. Miscellaneous	112	81	17	14

* Improvement in 1,021 cases (82.5%).
† No improvement in 107 cases (8.7%).
‡ Partial improvement in 109 cases (8.8%); despite disappearance of chief complaints, other minor symptoms persisted.
(Unpublished data obtained from Dr. H. Blüthgen.[6])

Medical and Other Personnel: Each group of 20 to 50 (30 on the average) trainees is supervised by one resident physician. These men are enthusiastically devoted to their task and contribute greatly to the morale of their wards by actively participating in many of the exercises. A few of them are endeavoring to collect objective data on the effectiveness of the reconditioning procedures.

Each center employs one to three gymnastic teachers and a number of secretaries, laboratory technicians, administrators, kitchen personnel, and servants.

Indications for Admission: Admission to a reconditioning center is recommended either by the prospective trainee's attending industrial plant physician or by his private doctor. The recommendation is usually based upon a statement made by the candidate himself and/or his immediate superior,

indicating a decline in his working performance and ability. It must be approved, as a rule, by an insurance physician of the respective organization.

The most common reasons for admission are abnormal fatigue; insomnia; irritability; and anxiety states, accompanied by neurovegetative cardiovascular manifestations such as "angina-like" symptoms, palpitations, lability of the blood pressure, cold extremities, and shortness of breath; bronchitides; vague gastrointestinal complaints; "rheumatic" aches; and,

TABLE 3

Results from Reconditioning

Response	Cardiac & Circulatory Symptoms: Vertigo, Cold Feet, Cardiac Complaints	Vegetative Symptoms: Inner Restlessness, Nervousness, Hyperhidrosis, Headaches	Symptoms of Upper Respiratory Tract: Cough, Expectoration, Dyspnea on Exertion	Gastrointestinal Symptoms: Stomach Complaints, Constipation, Anorexia	Rheumatic Symptoms, Especially Low Back Pain	Insomnia
	128	96	71	51	40	40
*Symptoms completely disappeared	83	31	37	26	21	19
†Markedly improved	19	41	15	11	7	7
‡Improved	21	16	9	9	6	7
	123	88	61	46	34	33
§No change	4	8	10	3	6	7
Worse	—	—	—	—	—	—
‖Newly acquired symptoms	1			2		
	5	8	10	5	6	7

* Symptoms completely disappeared in	50.9% of the cases.
† Markedly improved	23.6%
‡ Improved	15.9%
Total improvements	90.4%
§ No change	8.8%
‖ Newly acquired symptoms	0.8%
Total poor results	9.6%

After Schauwecker.[4]

very commonly, low back pain. The average age of the trainees in different centers ranges from 40 to 48 years.

Medical Results: In view of the diffuse and elusive nature of the trainees' symptoms, and due to medical staff limitations, no extensive, accurate statistics concerning objective results of the reconditioning procedures are yet available. Subjective reactions have been recorded in some of the centers (Tables 2, 3, 4).[4, 6, 7] These surveys provide a generally favorable impression, however, without definite conclusions. According to some preliminary statements, improvements of the Schellong work tolerance test,

TABLE 4

Subjective Data Obtained from 151 Women after Reconditioning*

Subjective improvement	90%
No change	10%
Improvement persisted:	
3 months	33%
6 months	40%
9 months	12%
More than 9 months	15%
Repetition declared desirable within:	
1 year	13%
2 years	76%
3 years	7%
4 years	1%

* After Stirn and Stirn.[7]

of the electrocardiogram, especially after exercise and in the erect position, of vital capacity (Table 5),[8] blood pressure, and skin circulation have been observed at the termination of reconditioning.[6, 9, 10–12] In a series of 40 factory workers with elevated blood pressure and signs of sympathetic overactivity, the statistically objective improvement persisted for an average of eight months.[41] The degree of active cooperation of the individual trainees in postreconditioning periods (home exercises and the like) was found to influence the persistence of beneficial after effects.[41]

It also seems significant that, despite the considerable physical strain which is gradually imposed on tens of thousands of trainees, and despite their frequent exposure to rough weather and to extreme temperature changes (sauna baths, standing under waterfalls), no major medical accidents have so far been reported. The acquisition of upper respiratory infections in the centers is said to have been negligible.

Economic Profitableness: From the point of view of the sponsoring industrial and insurance agencies, the question of long-range profitableness of the system in terms of improved working capacity, diminished medical expenditures, delayed invalidism, and reduced social security pension payments, is of paramount importance. Here again, after a total of seven years, and after three years of legally organized reconditioning practices, no detailed statistical data have yet been published. Nevertheless, none of the responsible industrial and insurance directors who were interviewed by this

TABLE 5

Responses of Respiratory Function to Reconditioning Procedures at Hillersbach Reconditioning Center*

	Improved	Unchanged	Worsened	Not Determined
Vital capacity	61.1%	27.2%	10.0%	1.7%
Pneumometry	61.9%	28.3%	6.2%	3.6%

* After Wieser et al.[8]

writer appeared to be skeptical regarding the economic advantages of the system. On the contrary, they referred to communications periodically received from trainees, insurance physicians, and foremen as justifying full confidence in the value of the existing reconditioning centers, and they expressed approval of the expanded construction of new ones.

According to one preliminary survey,[13] the earning capacity of the reconditioning trainees is generally improved, the morbidity is reduced, the age of beginning invalidism and even longevity is advanced. Between 1957 and 1959, 86.3% of the participants in the reconditioning program of one center remained free from illness, whereas the same individuals had been repeatedly ill before that period.[6]

It has been pointed out that the overall expense of creating one bed for a reconditioning trainee amounts to DM 12,000 to 22,000 ($3,000 to $5,500), that for a hospital bed DM 40,000 to 60,000 ($10,000 to $15,000).[10, 13] In addition, it has been argued[11] that the training of a skilled worker costs approximately DM 20,000 to 30,000 ($5,000 to $7,500), while the expenses for reconditioning require only fractions of these sums.

Several industries and insurance organizations are now systematically collecting data on the economic effectiveness of the reconditioning system for statistical evaluation in the future. Whatever the results may show, the German sponsoring agencies and legislators deserve credit for their farsightedness and courage in having followed the initiative of pioneering men like Kötschau,[14] Beckmann,[3] and Wahl,[15] and in investing large sums of money into a problematic experimental venture of great humanitarian and economic significance.

Scientific Exploitation of the Reconditioning System: The need for objective scientific evaluation of the empirically successful health preservation practices in the reconditioning centers is obvious. Aware of this fact, and realizing the wealth of information to be expected in the fields of physiology and psychology, a group of German scientists and clinicians, including guidance of the eminent physiologist, Professor Hans Schaefer of the University of Heidelberg, was recently formed in order to subject present reconditioning procedures to a thorough scientific scrutiny in cooperation with the respective resident medical staffs.

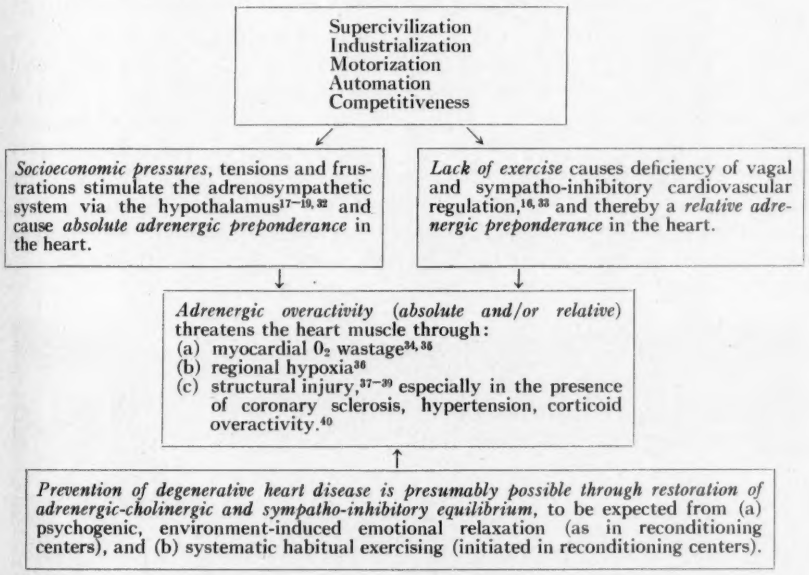
This writer, having been asked to serve as an external scientific consultant to the German Research Council feels that available modern technics should offer valuable findings. These should concern especially the area of neurovegetative cardiovascular interrelations under the impact of systematic exercising, in combination with the beneficial psychosomatic emotional effects of "getting away from it all," and with the subtle equilibrating influences of air, water, and light in a quiet rural environment. New reconditioning possibilities might thus be discovered, and a possible uncritical drifting toward faddish attitudes might be prevented.

Table 6 presents the neurovegetative mechanisms presumably responsible for the cardiac detriments resulting from supercivilized, tense, and physically inactive living, and the corrective influences to be elicited by reconditioning practices.

Beyond the conventional cardiovascular function tests, a variety of more specific neurovegetative testing procedures before and after reconditioning would appear to be desirable. Such procedures might include an investigation of the dynamic cardiac cycle (chronodynogram)[16] at rest and under standardized sensory and psychic stimulations, paralleled by assay of catecholamines,[17-19] corticoids, serum cholesterol, lipids and free fatty

TABLE 6

Schematic Representation of Neurovegetative Cardiopathogenic Mechanisms Resulting from Overcivilization, and Corrigible by Reconditioning Practices



acids,[18, 19, 20] blood clotting,[19] and blood viscosity.[21] Further studies might include electromyograms of tense muscle groups to observe their response to specific exercises, effect of physiotherapeutic measures (massage, heat, skin stimuli) upon "trigger points" and "soft tissue pain,"[22] and so on. Long-range statistical investigation of the lasting influence of reconditioning programs and indoctrinations on cardiovascular, muscular, and mental health should become possible with the steadily increasing number of trainees.

International Aspects: The success of the West German reconditioning centers over the past seven years has aroused so much international interest

TABLE 7

Established Medical Reconditioning Centers Abroad* and in United States

Country	Number of Centers	Number of Annual Admissions
USSR	2,500	5,000,000
East Germany	400	360,000
West Germany	15	15,000
Austria	1	1,000
USA	0	0

* The reconditioning centers in the Western and Central European countries are financed by insurance companies and industry, those in the Communist countries by governments.

that three similar, insurance-sponsored institutions were recently established, two in Switzerland and one in Austria. Delegates from Greece, Holland, Israel, Norway, and Yugoslavia have visited the German centers with the intention of introducing analogous methods into their own countries.

The apparent unfamiliarity of American medical professional, industrial, and insurance circles with the German system of health preservation may be explained, in part, by the fact that the American reader is virtually suffocated by the sheer volume of literature in his own language. However, in view of the present pointed emphasis on the need for international medical research and cooperation on health problems,[23, 24] the time seems ripe for this country to note the vigorous progress made in other nations in planning for public health preservation. It is worthy of note that some of those nations have taken the initiative, even though they are much less afflicted by the "diseases of civilization and prosperity" than are the American people (Table 7).

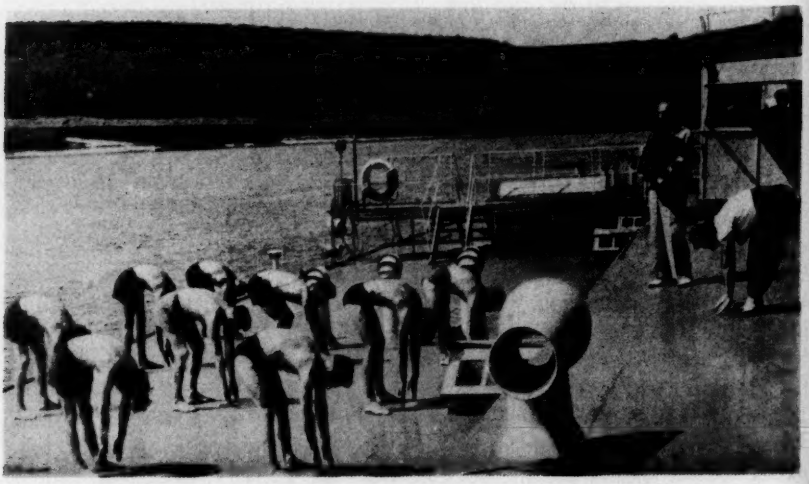


FIG. 5. Morning gymnastics with accordion accompaniment on the Russian floating reconditioning center "Gorky Commune." Reproduced from S. V. Kurashov and V. M. Zhdanov: "The Health of 200 Million People." (Courtesy World Health Bulletin, Geneva, May–June, 1960.)

In the Soviet Union, government sponsored reconditioning programs are applied in approximately 2,500 rural centers ("Kurorty") in the Caucasus, in the Ural Mountains, and on the Black Sea (Figure 5), and in the so-called "night sanatoria" of large industrial plants. The latter are special buildings on the premises where fatigued workers are accommodated during off duty hours for several weeks, and are subjected to physical and psycho-

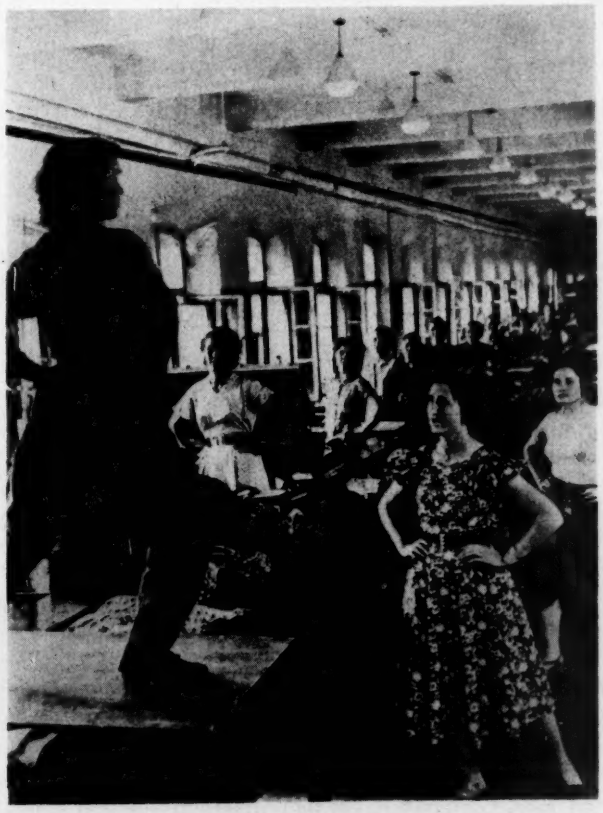


FIG. 6. Exercise break in a Soviet clothing workshop. Reproduced from S. V. Kurashov and V. M. Zhdanov: "The Health of 200 Million People." (Courtesy World Health Bulletin, Geneva, May–June, 1960.)

logic reconditioning practices. According to a statement made by the former Minister of Health, Mme. Kovrigina,[25] one cardiovascular death in the USSR occurs for 2.38 such deaths in the United States.

The Eastern German seven-year plan, based on legislation of 1957,[26] proposes to boost the annual 360,000 "cures" given in 400 reconditioning centers to an annual total of one million. Early prevention is increasingly

receiving priority over late rehabilitation in these programs. Exercise practices on the job (gymnastic breaks in the factories, and so forth) are generally encouraged (Figure 6).[27]

A more detailed report on technics and results of reconditioning systems in the Soviet Union and in other Eastern European countries will be presented at a later date. British physicians who recently visited Russian health centers were greatly impressed with the prevention-mindedness of Soviet medicine and were critical of those who are "so obsessed by curative medicine that they do not see the value of it." [28]

Need for Preventive Mass Reconditioning Programs in the United States. A recent survey concerning public opinion of the medical profession in this country [29] revealed discontent with its inadequate attention to the prevention of disease. A keen awareness of this deficiency was also expressed by Shields and Daitz,[30] who came to the following conclusions: "Organized medicine and official health agencies must develop methods designed to preserve functional capacity and delay the onset of disability. . . . The medical profession must become interested in stimulating the improvement and expansion of payment insurance plans to prevent disability and to reduce its effects."

It is to be expected that the example of European insurance organizations, industry, and governments in supporting vast preventive medical reconditioning programs will not remain unheeded much longer in this country. The superindustrialized, physically immobilized American people are more urgently in need of such public health protection policies than any other people, and the financial resources of the United States far surpass those available in the countries abroad which have been pioneering in this field for years.

Long-range financial considerations can only favor reconditioning systems that are intended to reduce the economic waste of manpower that results from the rampant "diseases of civilization." It seems significant that the huge reconditioning organization of the Soviet government under which some five million workers are sent to rural "Kurorty" each year, is operated with the explicit realistic intent to "safeguard maximal productivity." [31] The declared purpose of the rapidly expanding health reconditioning policies in communist East Germany is the determination "to beat capitalism now also in the field of economy." [27]

Obviously, it will not be possible or even desirable to adopt the administrative methods and procedural technics of the European reconditioning systems in this country without appropriate modifications. Not only is complete Soviet-style government financing out of the question; the mentality, motivation, and general physical condition of the future American trainees must be taken into account. In a somewhat arbitrary, generalizing fashion it may be said that the active participation of the average Russian worker in health preservation programs seems to be motivated primarily

by his indoctrinated feeling of duty to contribute toward the ultimate victory of his political creed. The German worker of today, no longer fanatically loyal to any clearly defined superpersonal cause, is still possessed by the typically Teutonic urge to maintain his full working capacity in order to justify his own existence. In the case of the American worker, an appeal to his desire for economic security for himself and his family might be the most effective approach when attempts at widespread manpower conservation are undertaken.

Furthermore, even some of the most elementary physical demands made on the less fit among the trainees in European exercise programs will probably be too strenuous for their American counterparts, and may have to be drastically reduced until higher standards of fitness are again attained. Careful medical supervision will be necessary to avoid disproportionate overtraining.

Competent and dedicated medical personnel will be needed for nationwide development of preventive reconditioning policies in this country. It can be obtained only if these men are not branded as freakish outsiders but are regarded as representatives and students of a legitimate and important new branch of preventive medicine.

The science and practice of late medical rehabilitation has assumed a rightfully respected position in the medical world. There is no logical reason why the slowly unfolding principles of early prevention should be denied an equal status in our present and future medical thinking, teaching, and acting.

Summary

During the past seven years, a system of preventive mass reconditioning (health preservation) has been developed in West Germany for the benefit of workers who are not yet overtly sick—employees and executives who are threatened by various "diseases of civilization," be they emotional, neurovegetative, cardiovascular, gastrointestinal, muscular, or postural.

Fifteen thousand persons are annually admitted to 15 rural reconditioning centers for four to six weeks without cost. These centers are located in attractive areas and are financed under federal law by insurance organizations and big industries. The participating trainees undergo systematically graded and closely supervised programs of outdoor physical exercises, hiking, and climbing, alternating with relaxation periods, physiotherapeutic applications, health instructions, and cultural entertainments.

Results in terms of subjective improvement, as well as in increased and prolonged working capacity and reduced morbidity, are said to be excellent, even though detailed statistical surveys have not yet been published.

The German reconditioning system is still being expanded, and eight other countries abroad have constructed or are planning similar insurance sponsored centers.

In the Soviet Union, mass reconditioning programs are carried out in

more than 2,000 government operated "Kurorty" and in industrial "night sanatoria." Eastern Germany has initiated a seven-year plan for the same purpose, namely, "to beat capitalism in the field of economy" through conservation of manpower and an increase in productivity.

A strong plea is being made for immediate preliminary establishment of pilot reconditioning centers in this country, equipped with facilities and staffs for scientific objective evaluation of some of the reconditioning methods practiced abroad. During the initial phase, investigative activities will have to be integrated with those of European research teams who have unlimited numbers of test subjects at their disposal.

The nationwide development of mass reconditioning programs in the United States is an urgent necessity. It should utilize the results of extensive objective investigations to be carried out under the sponsorship of official health agencies. The study and practice of early prevention of the "diseases of civilization" should become the subject of a new legitimate branch of preventive medicine, if we do not wish to lag further and further behind our more far-sighted opponents and friends alike.

Acknowledgments

The writer is obliged for assistance and cooperation in this survey to chief physicians of reconditioning centers (Drs. Beckmann, Blüthgen, Gerhards, Groh, Mauch, Meyer, von Nathusius, Rademacher, Rasbach, Schauwecker, Ufer, deWerth, and Wobbe); to insurance physicians (Drs. Carow, Claus, Lind and Schmidt); to industrial and social security directors (Messrs. Ball, von Hassel, Dr. Hoernigk, Kraft, Dr. Kraus, Neerforth, Meurer, and Wessel); to Ministerial Council Kissel; and to Prof. Hans Schaefer.

Summario in Interlingua

Le industrialisate nationes del Occidente se vide de plus in plus affligite de invalidante "morbos del civilisation" que resulta de inadequatia de exercitio physic, monotonia de travalio mechanic, pressiones e anxietates socio-economic, disillusionamento, vagantia spiritual, e tedio del vita. Le repercussiones neurovegetative physic e emotional de ille factores explica le alte incidentia de neuroses, de disturbationes gastrointestinal, metabolic, e muscular, e—particularmente—de casos de disveloppamento insidiose de alterationes degenerative in le systema cardiovascular. A parte disfavorabile habitudes dietari, iste imbalancias neurohormonal contribue fortemente al enorme incidentia de morbiditate cardiovascular e del mortalitate connectite con illo (55%) in le Statos Unite.

Le medicin curative e le technicas de rehabilitation ab le statos de morbiditate es altemente disveloppate in iste pais. Tamen, nulle effortios ha jam essite facite inter nos a organisar le preventive reconditionage in massa, per marcate contrasto con le extense systemas de reconditionage que es in servicios depost multe annos in altere partes del mundo, mesmo in paises ubi le desiderato de tal systemas es multo minus urgente que inter le americanos. In le U.R.S.S., Germania Occidental, Germania Oriental, Switza, e Austria, le governamentos, organisationes de assecurantia social, e le grande industria ha in servicio millenas de rural centros de reconditionage ubi omne anno milliones de obreros e empleatos es inviate pro periodos de exercitio, activitates sportive in plen aere, exercitios de respiration, relaxation psychologic, e indoctrination hygienic in un placente ambiente natural. Cinque altere paises es al puncto de inaugurar simile systemas.

Le centros e programmas de reconditionage in Germania Occidental es describite in detalio. Es formulate recommendationes pro le establimento de centros pilota de reconditionage a surveliantia medical in le Statos Unite e etiam pro projectos de recerca in le evalutation objective del resultatos immediate e a longe vista que pote esser effectuate per le diverse technicas specific de reconditionage. Es planate pro iste objectivo studios del reactiones cardiovascular e metabolic neurovegetative e etiam studios electromyographic.

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THE PERIODIC HEALTH EXAMINATION: EVALUATION OF ROUTINE TESTS AND PROCEDURES * †

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THE periodic health examination has been accepted as an effective means of detecting disease in asymptomatic people.[1-4] The type of examination in different clinics is generally similar and usually includes a group of tests and procedures that are carried out routinely.[1-5] Except for data provided by Bolt et al.,[6] the part played by each of these measures in determining the final diagnosis has received little attention in published reports. Although ultimate appraisal will require repeated observations of the same individuals over a period of years, we thought it useful to analyze our experience in order to provide objective data from which to select those routine tests and procedures which yield the greatest amount of information at the lowest cost.

The results of measures routinely included in the periodic health examination of the University of Pennsylvania Diagnostic Clinic constituted material for the present study. Determinations were made of the frequency with which each test was instrumental in establishing clinical diagnoses and the frequency with which they yielded false-positive or false-negative results. An analysis was also made of the cost of these measures in terms of the disease detected by them.

METHODS

Study Group: The material for this study was derived from the first periodic health examination of 1,500 persons who attended the Diagnostic Clinic of the University of Pennsylvania during the years 1948–1958. Some characteristics of this group of people and the nature and distribution of the diseases detected in them were the subject of a previous report.[7] The group consisted of males holding executive positions in 64 different companies and organizations located for the most part within 100 miles of Philadelphia. The average age was 45 years, with a range from 24 to 76 years.

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Tests and Procedures: The routine tests and procedures included hemoglobin determination; white blood cell count; examination of the urine for sugar, protein, red blood cells, and white blood cells; two-hour postprandial blood glucose value; serologic test for syphilis; 12-lead electrocardiogram; A-P x-ray of the chest; and sigmoidoscopic examination.

All laboratory tests were done in the Pepper Laboratories of the Hospital of the University of Pennsylvania. Hemoglobin values until October, 1955 were determined by the sodium carbonate technic, and thereafter by the cyanide method as described by Drabkin and recommended by the National Research Council. White blood cells were counted in the usual fashion by a laboratory technician. The presence of sugar in the urine was determined by Benedict's copper reduction test, and the presence of protein by the heat and acetic acid method. Centrifuged urine sediment was examined for white and red blood cells in the usual fashion. The level of blood glucose was determined by the Nelson-Somogyi method. The Kolmer and Kline technics were used for the serologic test for syphilis.

Electrocardiograms were read by senior staff members of the Cardiology Section of the hospital. A photofluorogram was taken initially on each patient and, if positive, was followed by a 14×17 chest film. All films were read by two radiologists. Sigmoidoscopic examinations were carried out by members of the general surgical staff.

Protocol: The clinical diagnoses recorded at the first examination of each patient, as conducted by Board-certified or eligible internists, were reviewed retrospectively, and these results, together with data obtained from each of the routine tests and procedures, were punched on cards for mechanical tabulation. Clinical diagnoses were made on the basis of the entire examination, which often included, in addition to the routine history, physical examination, tests, and procedures, other special consultations and studies deemed necessary by the examining physicians. These diagnoses were accepted as the best estimate of disease present in these people at the time of examination.

Definition of Abnormality: The findings were designated as normal or abnormal, as follows:

Hemoglobin values in the range of 12 to 17 gm. were considered normal until October, 1955, after which the normal range was 14.5 to 18.1 gm. because of a change in methods. White blood cell counts outside the range of 5,000 to 10,000 cells per cubic millimeter and two-hour postprandial blood glucose levels above 105 mg.% were designated abnormal. The presence of either protein or sugar in the urine and of either red blood cells or white blood cells in the urine sediment was designated abnormal. It was recognized that the report of an occasional red or white blood cell in the urine sediment could hardly be considered an abnormality in most circumstances. However, since no general agreement exists as to how many cells constitute an abnormality, it was thought best to consider the

report of any cells, either red or white, as an abnormality, realizing the obvious danger of overstating the positivity of these two tests in our studies.

The serologic tests for syphilis were designated abnormal when they were reported "reactive." The cardiologist's interpretation of the electrocardiogram was accepted as given. We were not concerned with how or why he arrived at his conclusions, but merely classified each interpretation as "normal" when it indicated a normal tracing, "qualified normal" when it indicated a borderline tracing or otherwise suggested an element of doubt as to its normality, and "abnormal" when it indicated a condition generally accepted as abnormal.

The x-ray of the chest was designated "abnormal" when the radiologist reported the presence of anything not considered to be the usual and accepted part of a chest x-ray. The sigmoidoscopic examination was designated "abnormal" only if it yielded evidence of colonic polyps or carcinoma. Other abnormalities, chiefly hemorrhoids, which were frequently reported, were not considered a significant finding in this study.

Having thus identified the results of various procedures to be considered outside the range of normal, five calculations were made: (1) the incidence of abnormal findings for each procedure in the group as a whole; (2) the frequency with which abnormal test findings appeared to determine the clinical diagnosis ("derived" diagnosis); (3) the frequency of abnormal test findings when, in view of the clinical diagnosis, normal findings could have been expected (false-positives); (4) the frequency of normal test findings when, in view of the clinical diagnosis, abnormalities could have been expected; (5) the cost per "derived" diagnosis of each procedure.

To make these calculations two of us (T.W.C. and K.O.E.) reviewed each diagnosis and made a judgment as to when each test could be expected to yield normal or abnormal results. For example, the chest x-ray in our opinion could have been expected to be abnormal when the final diagnosis was pulmonary tuberculosis, or the hemoglobin could have been expected to be abnormal when the final diagnosis was iron-deficiency anemia.

In attempting to determine to what extent an abnormal finding resulted in a clinical diagnosis, a distinction was made between a "derived" diagnosis and an "associated" diagnosis. A diagnosis was considered to have been "derived" from an abnormal test or procedure when, without it, the disease would not have been suspected or when the abnormal finding, though not necessarily specific for the disease, contributed materially to its discovery. For example, a diagnosis of diabetes mellitus was considered to have been "derived" from the finding of sugar in the urine.

An "associated" diagnosis was designated by us as being one in which an abnormal finding was either compatible with or usually encountered in the disease in question. For example, the finding of white blood cells in the urine of a person with benign prostatic hypertrophy, or the finding of cardiac enlargement in the chest x-ray of an individual with hypertensive

cardiovascular disease, was considered to be a compatible finding, but not diagnostic of the disease in question.

Determination of Cost Value: In determining a cost value for each test and procedure, the unit cost was that charged to the patient by the Diagnostic Clinic. The cost per "derived" diagnosis was determined by multiplying the unit cost by the number of patients in whom the measure was employed, then dividing the total cost for each procedure by the number of "derived" diagnoses credited to it.

Results

Test Results in Relation to Clinical Diagnoses: The frequency of abnormal findings (Table 1) in the 11 routine tests and procedures studied ranged from 1% in the case of urine protein and serologic tests for syphilis to a high of 57% in the case of leukocytes in the urine, where the presence of

Table 1

Frequency of Abnormal Test Findings

Test	Number of Persons Tested	Number of Persons with Abnormal Test Findings	Per Cent of Persons Tested Having Abnormal Test Findings
Urine WBC	1,490	855	57
WBC	1,442	332	22
Chest x-ray	1,481	289	20
Sigmoidoscopy	1,006	105	10
ECG	1,493	153	10
Blood glucose	1,244	129	10
Hb.	1,441	136	9
Urine RBC	1,490	66	4
Urine sugar	1,490	55	4
Serologic test for syphilis	1,500	13	1
Urine protein	1,490	14	1

any leukocytes was regarded as abnormal. Glycosuria and red blood cells in the urine sediment were also rarely noted (4%). Other tests were abnormal in 10 to 22% of individuals tested.

The frequency with which abnormal findings appeared to influence the clinical diagnoses varied widely (Table 2). For example, clinical diagnoses were, by definition, derived from the sigmoidoscopic examination in 100% of the people having the abnormal findings listed on this procedure, whereas in less than 0.5% of the people with white blood cells in the urine did this finding serve to establish a diagnosis. Sugar in the urine resulted in a diagnosis in roughly one-half of the patients with this abnormality; deviations from the normal in the electrocardiogram led to a diagnosis in one-third of those having such abnormalities; and abnormalities in the chest x-ray led to a diagnosis in approximately one-fifth of those with findings outside the range of normal. Among the other tests, abnormal findings led to diagnoses in from zero to 8% of those in whom such findings occurred.

TABLE 2

Frequency of Diagnoses Derived* from Abnormal Test Findings

Test	Number of Persons with Abnormal Test Findings	Number of Persons Having Diagnoses Derived from Abnormal Test Findings	Per Cent of Persons with Abnormal Test Findings Having Derived Diagnoses
Sigmoidoscopy	105	105	100
Urine sugar	55	26	47
ECG	153	46	30
Blood glucose	129	31	23
Chest x-ray	289	61	21
Serologic test for syphilis	13	1	8
Urine protein	14	1	7
Hb.	136	3	2
WBC	332	2	1
Urine WBC	855	1	†
Urine RBC	66	0	0

* A clinical diagnosis was considered to have been "derived" from the abnormal test findings when, though not necessarily specific for the disease, the test contributed materially to its discovery or when, without the test, the presence of the disease would not have been suspected. Such clinical diagnoses were either of known disease or newly discovered disease.

† Less than 0.5%

No correlation existed between the frequency with which abnormal findings were detected in the total population by any given measure and the frequency with which that finding established diagnoses.

A total of 278 diagnoses was considered to have been derived from all of the 11 routine tests and procedures employed. Five of these measures, namely, sigmoidoscopy, urine sugar, electrocardiogram, two-hour postprandial blood glucose, and chest x-ray, accounted for 270 (97%) of the diagnoses. The other six measures together led to only eight (3%) of all the derived diagnoses.

When the criterion of association between the abnormal test finding and

TABLE 3

Frequency of Abnormal Test Findings without Associated* Diagnoses (False-Positives)

Test	Number of Persons with Abnormal Test Findings	Number of Persons with Abnormal Test Findings without "Associated Diagnoses"	Per Cent of Persons with Abnormal Test Findings Having No Associated Diagnoses
Sigmoidoscopy	105	0	0
ECG	153	66	43
Urine protein	14	6	43
Urine sugar	55	29	53
Chest x-ray	289	187	65
Blood glucose	129	98	76
Hb.	136	123	90
Urine RBC	66	60	91
WBC	332	302	91
Serologic test for syphilis	13	12	93
Urine WBC	855	801	93

* An "associated" clinical diagnosis was one in which an abnormal test could be considered either compatible with or usually encountered in a given diagnosis.

the final diagnosis was broadened to include all diagnoses with which the abnormal test finding might be compatible, as well as those diagnoses established by it (Table 3), (with the exception of sigmoidoscopy, the electrocardiogram, and the finding of protein in the urine), the majority of persons with abnormal test findings had no diagnoses with which these findings could be associated. Thus, the percentage of false-positive findings was remarkably high for most of the routine diagnostic measures.

When those persons were identified whose diagnoses carried the expectation of an abnormal test finding, even though there was a wide range in the frequency with which the expected abnormality was absent (false-negative, Table 4), in four procedures no false-negative occurred and in all others, except for red blood cells and protein in the urine, a false-negative occurred in 50% or less of the examinations.

TABLE 4

Frequency of Normal Test Findings in Persons with Diagnoses Carrying Expectation of an Abnormal Test Finding (False-Negative)

Test	Number of Persons with Diagnoses Carrying Expectation of an Abnormal Test Finding	Number of Persons with Such Diagnoses Having a Normal Test Finding	Per Cent of Persons with Such Diagnoses Having a Normal Test Finding
WBC	2	0	0
Serologic test for syphilis	1	0	0
Chest x-ray	37	0	0
Sigmoidoscopy	105	0	0
Blood glucose	35	4	11
Urine WBC	10	2	20
Hb.	4	1	25
ECG	22	10	45
Urine sugar	50	25	50
Urine protein	7	6	86
Urine RBC	10	9	90

Hemoglobin: Of the hemoglobin determinations made on 1,441 persons, 43 (3%) were below normal, and 93 (6.4%) were above normal. However, only two persons with hemoglobin values below normal were diagnosed as having anemia. One of these, with a value of 10.9 gm., recently had donated blood, and this was considered to be the cause of the anemia. The other, with a value of 11.5 gm., was diagnosed as having anemia of unknown cause.

Of the 93 persons with hemoglobin values above normal, a diagnosis of polycythemia vera was made in only one, who had a value of 17.8 gm.

White Blood Cell Count: The white blood cell count was made on 1,484 persons; 198 (13.4%) had more than 10,000 white cells per cubic millimeter, while 134 (9%) had less than 5,000 per cubic millimeter. No person had a recorded diagnosis related to a low white blood cell count. Of those with counts over 10,000, in only two cases were the elevated white cell counts considered to have been helpful in detecting the presence of the disease.

These were a subsiding acute trachebronchitis with a white count of 11,800, and an ill-defined chest disease, cause undetermined, with a white count of 24,600.*

Routine Urinalysis: Routine urinalyses were made in 1,490 persons. Protein was found in the urine of 14 of these persons. Of these, eight were found to have conditions which could account for the presence of the protein, seven being hypertensive and one having a chronic urinary tract infection. In one of the hypertensives the finding of urinary protein helped to establish a diagnosis of malignant hypertension; in the others it did not appear to contribute to the diagnosis.

Fifty-five persons had sugar in the urine, but the diagnosis of diabetes mellitus was made in only 26. Of these 26 persons, the disease was newly detected in 17.

Sixty-four persons were found to have red blood cells in the urine. Of these, six had diagnoses which were considered compatible with this finding. However, in none was the diagnosis considered to be derived from this finding alone.

White blood cells were found in the urine of 855 persons. Fifty-four of these had diagnoses which were considered compatible with this finding. However, in only one of these was a diagnosis (pyuria) thought to have been made solely on the basis of the finding.

The other elements of the urinary sediment did not appear to be involved in any of the diagnoses made in this study.

Serologic Tests for Syphilis: A serologic test for syphilis was made on 1,500 persons and was found to be abnormal in 13. In one of these, the diagnosis of a previously known, latent syphilis was substantiated. Among the remaining 12 persons with positive serologic reactions, no diagnoses were made compatible with this finding. Seven have been re-examined at intervals of a year or more. Of these, four have developed negative reactions and three have continued to show positive reactions. However, in none of these three persons was a diagnosis of syphilis or of a biological false-positive result made by the examining physician.

Blood Glucose Determinations: A two-hour postprandial blood glucose determination was made in 1,244 persons. Of these, 129 (10%) had levels greater than the accepted upper limit of 105 mg.%. In only 31 persons was the diagnosis of diabetes mellitus made, in 20 of them for the first time. Among the previously unrecognized diabetic persons, nearly one-half had blood glucose levels above 120 mg.% without glycosuria, while two had blood glucose levels of less than 105 mg.% accompanied by glycosuria. The diabetic state can be overlooked if one relies on either the blood glucose level or the urinalysis alone.

* The persons whose examinations made up the material for this study included only those who came to the Clinic as part of a periodic health examination program during the years 1948–1958. Since 1958 one person has come through the Clinic on such a program whose white blood count and blood smear led to the diagnosis of chronic lymphatic leukemia.

TABLE 5

Percentage Distribution of 1,493 Persons with and without Heart Disease Having Various Electrocardiographic Findings

Electrocardiogram	Heart Disease	No Heart Disease	All
No. of people	272	1,221	1,493
Normal	55	84	78
Qualified normal	12	11	12
Abnormal	33	5	10
Total	100	100	100

Electrocardiogram: An electrocardiographic tracing was obtained in 1,493 persons. It was abnormal in 153 (10%) and normal or "qualified normal" in 90%. However, of those patients with clinical diagnoses of heart disease (Table 5) over one-half showed no changes in the electrocardiographic tracings suggestive of heart disease. Conversely, 5% of those without clinical evidence of heart disease had electrocardiographic tracings considered to be abnormal.

In those with diagnoses of heart disease (Table 6) the electrocardiogram was most apt to be abnormal (82%) in the presence of functional cardiac abnormalities (which included all disturbances in rhythm), and least apt to be abnormal (25%) in the presence of hypertensive heart disease. Approximately half of those with the diagnosis of arteriosclerotic heart disease showed abnormalities in the electrocardiogram, while less than half of those with rheumatic heart disease did so.

In assessing the effectiveness of the electrocardiogram as a detector of disease, it will be seen from Tables 1, 2, and 3 that it is among the most effective of the tests routinely employed. In 30% of persons with abnormal electrocardiograms, the finding contributed to the final diagnosis. The false-positives were fewer (43%) than for the majority of the tests. On the other hand, the frequency of normal electrocardiograms in the presence of diagnoses carrying the expectation of an abnormal record (false-negative) was higher (45%) than for all but three of the other tests and procedures.

Chest X-ray: An x-ray of the chest was obtained in 1,481 persons. The 20% of abnormal reports (Table 1) constituted one of the highest yields

TABLE 6

Percentage Distribution of Electrocardiographic Findings in 1,493 Persons by Type of Heart Disease

Electrocardiogram	No Heart Disease	Hypertensive	Arteriosclerotic	Rheumatic	Functional	Other
No. of people	1,221	193	49	11	28	11
Normal or "qualified normal"	95	75	47	55	18	46
Abnormal	5	25	53	45	82	54
Total	100	100	100	100	100	100

of abnormality for any of the procedures employed, yet only approximately one-fifth of these were instrumental in establishing a diagnosis (Table 2). Since an x-ray reveals not only active lesions important to the present health of an individual but also evidence of healed and inactive lesions no longer of importance, it is of interest to note that of the 61 diagnoses derived from these reports, only 26 were thought to indicate active disease.

In terms of the performance of the total battery of tests and procedures, the chest x-ray ranks below the sigmoidoscopy, but in our experience is one of the more effective procedures. Frequently, however, positive findings on the chest x-ray were considered clinically unimportant, and in the absence of a clinical diagnosis are included in the false-positives (Table 3). However, in no persons did the chest x-ray fail to reveal pathology in whom

TABLE 7

Cost of Various Tests and Procedures per "Derived" Diagnosis*

Test	Number of Persons Tested	Cost per Test	Total Cost	Number of "Derived" Diagnoses	Cost per "Derived" Diagnosis
Urinalysis	1,490	$ 1.50	$ 2,235.00	28†	$ 79.82
Blood glucose	1,244	3.00	3,732.00	31	120.39
Chest x-ray	1,488	5.00	7,440.00	61	121.77‡
Sigmoidoscopy	1,006	15.00	15,090.00	105	143.71
ECG	1,493	8.00	11,944.00	46	259.65
Hb.	1,441	1.50	2,161.50	3	720.50
WBC	1,484	1.50	2,226.00	2	1,113.00
Serologic test for syphilis	1,500	3.00	4,500.00	1	4,500.00

* A clinical diagnosis was considered to have been "derived" from the abnormal test findings when, though not necessarily specific for the disease, the test contributed materially to its discovery, or when, without the test, the presence of the disease would not have been suspected. Such clinical diagnoses were either of known disease or newly discovered disease.

† Includes diagnoses derived from all components of the urinalysis, namely tests for sugar, protein, white and red blood cells.

‡ If only derived diagnoses important to the well-being of the individual are considered, the cost per derived diagnosis rises to $349.46.

the clinical diagnosis carried an expectation of such pathology. There were, in other words, no false-negatives (Table 4).

Sigmoidoscopic Examination: A sigmoidoscopic examination was performed on 1,006 persons in this group. The incidence of abnormal findings, which for the purposes of this study were limited to the finding of rectal polyps (10%) and carcinoma, was similar to that reported in other health surveys.[8-10] Since the diagnosis in each instance was made on the basis of the visualization of intestinal polyps by the sigmoidoscopist, and since there is no other way of determining the presence or absence of these lesions, there were no false-positive or false-negative results attributed to this procedure (Tables 3 and 4). Except for five persons who gave a history of rectal bleeding, no symptoms, clinical signs, or other procedures suggested the presence of this abnormality. Carcinoma in the polyp was established by biopsy in three instances.

Cost Analyses: Inspection of the cost of the various tests and procedures, compiled as described above, reveals that, when considered in relation to the helpfulness of each in arriving at diagnoses, some of them are exceedingly expensive (Table 7). Thus, some of the initially cheaper tests, such as the hemoglobin, white blood cell count, and serologic test for syphilis, emerge as far more costly, in terms of usefulness in arriving at diagnoses, than do initially more expensive tests, such as the chest x-ray, electrocardiogram, and sigmoidoscopy. Actually, the most expensive test, the sigmoidoscopy, was in reality among the cheapest in terms of cost per derived diagnosis.

Discussion

In attempting to assess the usefulness of certain tests and procedures as routine parts of the periodic health examination we have concerned ourselves primarily with the role of abnormal test findings in determining clinical diagnoses. We recognize that there are other criteria of usefulness which may be applied. Among these, the value of a normal test finding, by ruling out the presence of disease, may be considerable. However, in a retrospective study, objective evaluation of this aspect of usefulness was not possible.

The routine procedures which we employed yielded abnormal results with widely varying frequency, and very often these abnormal results appeared not to influence the final diagnosis. Six of the tests—the detection of protein and red and white blood cells in the urine, the hemoglobin determination, the white blood cell counts, and the serologic test for syphilis—despite widely varying frequency of abnormal results, appeared to influence the diagnosis in so few instances that we believe their omission as routine procedures would not seriously have decreased the effectiveness of the examinations.

On the other hand, the sigmoidoscopic examination, the test for sugar in the urine, the two-hour postprandial blood glucose determination, the electrocardiogram, and the chest x-ray when reported abnormal, led to diagnoses more consistently. We concluded, therefore, that these five measures contributed sufficiently to our examinations to be regarded as useful routine procedures.

We were astonished to observe that the prevalence of false-positive results was remarkably high for all the routine tests and procedures except the sigmoidoscopic examination, even when we broadened the criterion of relationship between abnormal results and final diagnoses to include all diagnoses with which the abnormal findings might be compatible. In other words, the majority of persons with abnormal test findings had no diagnoses with which these findings seemed to be associated and, with the sole exception of those obtained by sigmoidoscopy, the examining physicians disregarded or judged to be noncontributory over 50% of these abnormal findings. These observations have led us to question whether the so-called

normal ranges for the measures studied are applicable to a healthy population such as ours. More data from such populations are desirable.

Our evaluation of the effectiveness of these measures has been based on the final diagnosis made by the examining physician, arrived at by the totality of methods used in the examination. Thus, the role of the individual examiner assumes great importance. The physicians conducting the examinations were given no common standards for arriving at any one diagnosis. They comprised a cross section of well-trained and modern physicians in a university medical center. To us, one of the most striking aspects of this study has been the disclosure of an apparently arbitrary acceptance or rejection of abnormal laboratory reports by these examiners. For example, when we analyzed the relationship between the blood glucose value and the clinical diagnosis of diabetes mellitus (Figure 1) we found that, among known diabetics, the diagnosis of diabetes mellitus was apparently accepted by the examiner regardless of the blood glucose level, whereas among those persons with elevated blood glucose levels in whom

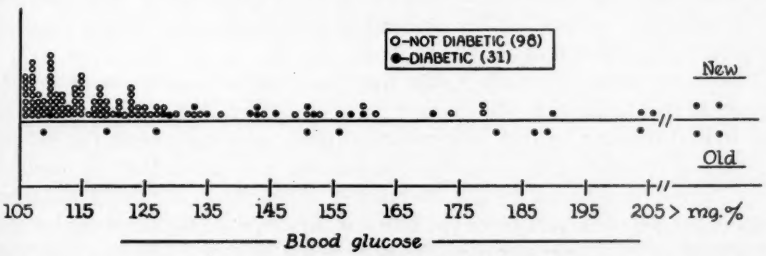


FIG. 1. A frequency distribution of 129 persons whose blood glucose levels were over 105 mg.%, with and without diagnoses of diabetes.

diabetes had not previously been diagnosed, there was no consistency between the level of blood glucose and the examiner's decision with regard to the diagnosis. Thus, it was impossible to surmise why one individual in this group with a blood glucose level of 150 mg.% was considered to be diabetic, while another with the same level was not so diagnosed.

In retrospect, it is impossible to determine how an examiner arrived at a diagnosis and how he interpreted laboratory reports. He may have discarded an abnormal report for any one of a number of reasons. His estimate of the limits of normality of the test may have differed from those that were adopted by us in our analysis of the data; he may have refused to make a diagnosis on the basis of a single laboratory finding, or he may have attributed the abnormal finding to some physiological variation or laboratory error. Whatever his reasons, he apparently felt free to interpret the abnormal results as he saw fit. This fact introduces an unmeasurable "observer difference" into our data. At the same time, it sheds an interesting light on physician performance.

The paucity of false-negative results observed by us seems to confirm our impression that, in general, if an abnormal report supported a clinical suspicion, it was accepted by the examiner, whereas if it came as an unexpected finding it might well be rejected. Unfortunately we cannot determine from this study how often a normal report led to the rejection of a clinical suspicion.

The frequent occurrence of normal electrocardiographic tracings in the presence of clinically diagnosed heart disease and, conversely, the finding of abnormal tracings in a substantial proportion of those without clinical evidence of heart disease, were surprising findings for which we at present have no explanation. Further studies of these persons are under way.

The cost of these tests and procedures per derived diagnosis deserves some comment. Such calculations point up the fallacy of selecting tests on the basis of cost since, as we have pointed out, some of the apparently "cheaper" tests are actually extremely costly in terms of their usefulness in arriving at a clinical diagnosis. However, this should not obscure the fact that, since the objective of periodic health examinations is to preserve health, negative results, by demonstrating the absence of disease, have an important though unmeasurable value.

We have based our study on the first examination of our subjects. An abnormal test finding in the absence of a corresponding clinical diagnosis may indeed represent a true false-positive result, or it may, with the passage of time and repeated observations of the patient, be found to have represented early disease undetected by the examining physician. Repeated examinations of the persons who form the basis of this report have been under way for a number of years, and data are now being analyzed which should add to our understanding of the value of these routine measures.

We are currently testing a number of additional procedures to assess their usefulness in identifying disease in asymptomatic persons. We hope our findings will add to the effectiveness of the periodic health examination.

Summary

Eleven tests and procedures included routinely in the periodic health examinations of 1,500 individuals conducted at the Diagnostic Clinic of the University of Pennsylvania were studied to determine the frequency of abnormal findings, the frequency with which abnormal findings were instrumental in arriving at final diagnoses, and the cost in terms of "derived" diagnoses. There appeared to be no correlation between the frequency of findings outside the range of normal and the frequency with which these findings were instrumental in arriving at final diagnoses, while the occurrence of false-positive findings was remarkably high.

The determination of protein and red and white blood cells in the urine, the hemoglobin determinations, the white blood cell counts, and the serologic tests for syphilis appeared to influence the diagnosis in so few instances that

their omission as routine measures would not have significantly reduced the effectiveness of our examinations. On the other hand, the sigmoidoscopic examination, the test for sugar in the urine, the two-hour postprandial glucose determination, the electrocardiogram, and the chest x-ray contributed sufficiently to the final diagnoses to be regarded as useful routine procedures.

A surprising finding was the degree to which physicians disregarded abnormal test results in arriving at diagnoses. The possible reasons for this are discussed, together with the bearing which this has on the interpretations we have made.

The "cheaper" tests frequently emerged as the more expensive ones when viewed in terms of effectiveness in identifying disease.

Summario in Interlingua

Esseva studiate certe tests e procedimentos communmente includite in le routine del periodic examine sanitari, con le objectivo de determinar le quales inter illos es le plus utile in establir le diagnose final. Il es solmente per medio de tal studios que il es possibile—in nostre opinion—determinar le quales del varie mesuras deberea esser retenite como parte routinari del examine in question.

Le presente studio esseva facite a base del constatationes clinic e laboratorial de 1.513 personas qui participava in le programma de periodic examine sanitari del Clinica Diagnostic al Universitate Pennsylvania. Esseva analysate le resultatos del determination de hemoglobina; del numeration de leucocytos; del examine del urina pro sucro, proteina, erythrocytos, e leucocytos; del concentration de glucosa postprandial in le sanguine; del tests serologic pro syphilis; del electrocardiogramma; del roentgenogramma thoracic; e del studio sigmoidoscopic. Iste diverse tests e procedimentos esseva evalutate a base del constatationes de anormalitate facite per medio de illos, del contribution facite per illos al ultime diagnose clinic, e del costos causate per illos.

Esseva concludite que, in le population studiate, le tests serologic pro syphilis contribueva pauco; que le urinanalyse esseva utile in certe casos, specialmente quando illo revelava le presentia de glycosuria; e que etiam le determination de hemoglobina e le numeration de leucocytos esseva utile in certe casos solmente. Le utilitate del determination postprandial de glucosa in le sanguine, del electrocardiogramma, del roentgenogramma thoracic, e del sigmoidoscopia esseva clarmente demonstrate.

Un alte procentage de resultatos falsemente positive esseva incontrate pro omne le procedimentos con le exception del sigmoidoscopia. Esseva opinate que iste constatation indica que le medicos non reguarda un resultato anormal per se como base sufficiente de un diagnose clinic.

Quando le costo del diagnose individual que esseva establite a base de constatationes anormal in le tests e procedimentos studiate esseva calculate, il esseva trovate que certes del tests, per exemplo urinanalyses e determinationes del leucocytos es multo costose.

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CLINICAL PATHOLOGICAL CONFERENCE

DIFFERENTIAL DIAGNOSIS OF MITRAL REGURGITATION IN CHILDHOOD: CLINICAL PATHOLOGICAL CONFERENCE AT THE NATIONAL INSTITUTES OF HEALTH *

Moderator: EUGENE BRAUNWALD, M.D. *Discussants:* RICHARD S. ROSS, M.D., F.A.C.P., *Baltimore, Maryland;* ANDREW G. MORROW, M.D., and WILLIAM C. ROBERTS, M.D., *Bethesda, Maryland*

DR. EUGENE BRAUNWALD: The patient whose records form the basis of this conference taught a good deal to those of us who were involved in his care, and for this reason his case was selected for this presentation.

He was a 13-year-old colored male who was the product of a normal full term pregnancy and delivery and who weighed over six pounds at birth. His growth and development were retarded, walking occurring at 18 months and talking after the age of two years. His mother felt that he had always been small and sickly compared with his siblings.

He was not examined by a physician until the age of six years when he was hospitalized because of fever and tachypnea. Physical examination revealed a pulse of 108, and blood pressure of 120/75 mm. Hg. The lungs were clear. A grade IV, high pitched, systolic murmur was heard at the apex; there was a protodiastolic sound at the apex and a questionable presystolic murmur at the apex. Chest x-rays revealed cardiomegaly with a cardiothoracic ratio of 0.61. The left ventricle was considered to be greatly enlarged and there was slight fullness in the area of the pulmonary conus. The electrocardiogram was said to show prolongation of the PR interval when age and rate were considered. Acute rheumatic fever was diagnosed and, following discharge from the hospital, the patient was placed on oral penicillin. Examination eight months later showed a regular rhythm, a systolic thrill and loud systolic murmur at the apex, and a questionable presystolic murmur at the apex. The electrocardiogram showed a PR interval of 0.19 sec. and a heart rate of 110/min.

He convalesced slowly but was not able to resume normal activity. He was hospitalized near his home four times because of fever, with abdominal pain on one occasion, and symptoms of left and right sided heart failure on three occasions. His C-reactive protein and antistreptolysin titer were always unremarkable. Cardiac examination always revealed systolic and diastolic murmurs, and during the latter two hospitalizations he was in atrial fibrillation which converted to sinus rhythm upon

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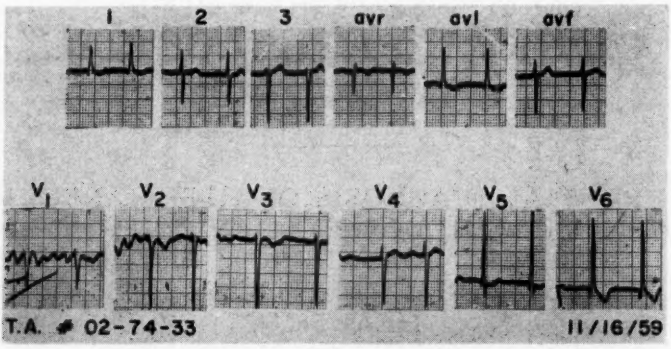


FIG. 1. Electrocardiogram of patient T. A.

administration of quinidine. The electrocardiograms showed left atrial and ventricular enlargement with a first degree heart block.

He was referred to the National Heart Institute because of persistent dyspnea and orthopnea. On physical examination the patient was a small, poorly developed, undernourished boy who appeared to be chronically ill. Blood pressure was 110/87 mm. Hg and the pulse rate was 100/min. and grossly irregular. The neck veins were dilated and pulsated vigorously when he was in the sitting position. There was a prominent precordial bulge, a striking left ventricular lift, and a modest right ventricular lift. The second heart sound was palpable along the left sternal border. On auscultation this sound was split with a loud pulmonic component. The phonocardiogram showed that P_2 remained split even after the Valsalva maneuver. A grade 3/6 pansystolic murmur was best heard at the apex but was well transmitted to the axilla and over the entire precordium. A grade 3/6 mid-diastolic, rumbling



FIG 2. Chest roentgenogram of patient T. A.

murmur and an early diastolic sound were heard at the apex. The liver edge was palpable five fingerbreadths below the costal margin. The complete blood count, sedimentation rate, serology, urinalysis, CRP, ASO, blood electrolytes, and "liver chemistries" were unremarkable. The electrocardiogram is reproduced in Figure 1 and the chest roentgenograms in Figures 2 and 3.

Our discussant today is Dr. Richard S. Ross, Associate Professor of Medicine and Radiology at the Johns Hopkins University School of Medicine. Dr. Ross had only the above protocol on hand for the preparation of his initial discussion.

DR. RICHARD S. ROSS: The electrocardiogram shows left axis deviation and atrial fibrillation. There is no R wave in Lead V_1. Deep S waves are present over the right precordium. The R wave is 24 mm. in Lead V_6, and small Q

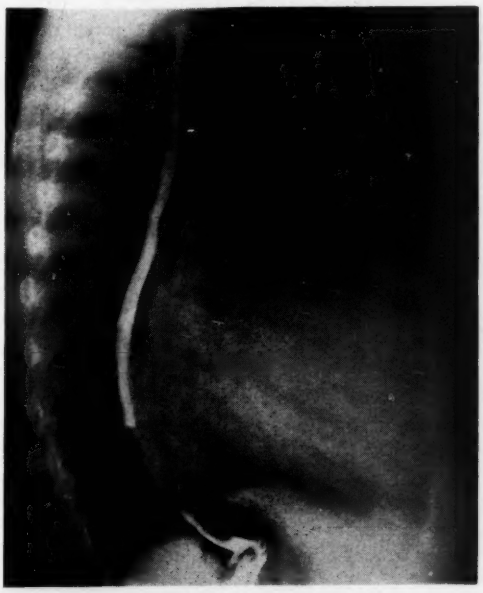


FIG. 3. Lateral roentgenogram of patient T. A.

waves are present over the left precordium. The sagging of the ST segments and inversion of T waves in Lead V_6 are characteristic of left ventricular hypertrophy or, in older terminology, "left ventricular strain." On the roentgenograms the heart is huge and there appears to be enlargement of all chambers. There is fullness in the region of the pulmonary artery and there is a double density which I believe represents the left atrium. I think the little prominence on the right border of the heart is also part of a giant left atrium. In the lateral and right oblique views, there is posterior deviation of the esophagus, which makes me feel that this individual had a greatly enlarged left atrium. In the right oblique projection, the left atrium bulges out behind the esophagus. The left oblique film shows the left ventricle to be enlarged and it is seen to project posteriorly well beyond the spine. In summary, the x-rays show enlargement

of the left atrium and left ventricle and slight fullness of the right ventricular outflow tract.

There was an excellent history of retarded growth and development which can be used to support the contention that the disease was congenital. The febrile illness may or may not be significant, but it could have been either rheumatic fever or bacterial endocarditis. The most prominent physical sign was a loud apical pansystolic murmur which was noted by several observers. It was heard maximally at the apex, but also at other places on the precordium. Throughout the history there was evidence of both right and left ventricular failure. The patient was dyspneic and tachypneic, but he also had a large liver and distended neck veins.

Occasionally, the heart may be enlarged, or may function abnormally from extracardiac causes, and this possibility must always be considered first. In this case we can say, from the size of the heart and other findings, that this individual had primary heart disease. The intensity of the murmur and the coexisting thrill makes me feel certain that this patient had either valvular disease, a septal defect, or obstruction to the outflow tract in one or the other of the cardiac chambers. A murmur of this intensity, associated with a thrill, is not heard in the absence of one of these recognized causes of turbulence within the heart.

We next come to the question of whether this be congenital or acquired heart disease. The early appearance of the murmur and the retarded growth and development indicate that it was congenital heart disease. It is possible to have rheumatic fever at an early age. We have seen a patient recently with mitral insufficiency who had unequivocal chronic rheumatic valvular disease at the age of six years, but this is not the usual situation. There were no associated manifestations of rheumatic fever in the case under discussion today and the laboratory studies for detecting active rheumatic fever were negative. In difficult clinical situations such as this, the C-reactive protein and antistreptolysin titer are most useful when they are negative. At this point, rheumatic heart disease can be eliminated from consideration, and the patient can be considered to have had congenital heart disease.

We then have to reconsider the two general categories of diseases in which murmurs of this intensity are heard—septal defects and valvular diseases. On the x-rays the lung fields did not appear to be abnormally vascular. The electrocardiogram showed no evidence of right ventricular hypertrophy or right axis deviation, and I was unable to explain the giant atrium on the basis of any of the well known septal abnormalities. I considered ventricular septal defect, atrial septal defect, a shunt from the left ventricle to the right atrium, and a patent ductus arteriosus. I did not give specific consideration to right-to-left shunts because no mention was made of cyanosis.

The ostium primum defects and the varieties of persistent common atrioventricular canal receive special attention because these defects are frequently associated with mitral valve abnormalities. The electrocardiogram in the ostium primum defects always shows some evidence of right ventricular hypertrophy, and this was lacking in today's patient. Furthermore, the left atrium is never enlarged to this degree. These two facts allowed me to eliminate ostium primum defects from this initial discussion.

The left ventriculo-right atrial communications were considered with Dr.

Braunwald's article as the reference.[1] The electrocardiogram in his patients showed right ventricular hypertrophy, combined hypertrophy, or ". . . a suggestion of left." Thus, left axis deviation and left ventricular hypertrophy were inconsistent with ventriculo-atrial shunt. Left atrial enlargement would not be expected in these patients and it was not present in the reported patients. At this point I eliminated all the common and uncommon left-to-right shunts.

The category of valvular and obstructive lesions must be considered next. Because of the massive dilatation of the left atrium and the left ventricle, attention was directed to the left side of the heart. Valvular aortic stenosis seemed an unlikely cause of this murmur. Subvalvular aortic stenosis could produce a murmur in this location. We have seen a few cases of a subvalvular obstruction in which the murmur was maximal at the apex or near the apex; in one case, there was a thrill at the apex in association with the murmur.

In favor of the diagnosis of subvalvular aortic stenosis, we might list the signs of left ventricular hypertrophy on the electrocardiogram and the large left ventricle on the x-ray. The left atrium may be enlarged in aortic stenosis but I have never seen a left atrium attain the size which our patient's did in the presence of aortic stenosis alone. Therefore, against the diagnosis of aortic

TABLE 1

Congenital Mitral Insufficiency

1. Fused fixed valve.
2. Cleft mitral leaflet.
3. Perforated mitral leaflet.
4. Double orifice of the mitral valve.
5. Anomalous insertion of chordae tendineae.
6. Corrected transposition of great vessels
   a. Anomalous insertion of chordae tendineae.
   b. Ebstein's malformation, left.
7. Fibroelastosis of left ventricle.

stenosis would be this tremendous enlargement of the left atrium and the description of the murmur as pansystolic. This is unusual even for the murmurs in subaortic stenosis which are usually confined to the early part of systole. Obstruction to left ventricular outflow did not offer an adequate explanation for all the important findings and therefore was excluded.

Mitral insufficiency, the other cause of murmurs of this type, offered the best explanation for the enlarged left atrium. The left atrium may reach this size in mitral stenosis, but the more common cause of giant atrium is mitral insufficiency. The signs of left ventricular hypertrophy on physical examination, the enlarged left ventricle on x-ray, and the electrocardiographic findings were perfectly compatible with this diagnosis. The murmur was much more compatible with mitral insufficiency than it was with aortic stenosis.

I had some reservations about the electrocardiogram because, though left axis deviation and left ventricular hypertrophy occur in mitral insufficiency, the axis is usually not much to the left of 0°. Furthermore, this particular type of ST segment is uncommon in mitral insufficiency. There were minor objections and I concluded that congenital mitral insufficiency was the best diagnosis.

This led to a consideration of the various anatomic lesions which result in mitral regurgitation (Table 1).

The literature contains descriptions of valves with fused, fixed cusps, valves with a cleft leaflet in association with the ostium primum defect and without this lesion, perforated valve leaflets, valves with a double orifice, and cusps with anomalous insertion of the chordae tendineae in such a way as to hold the valve open. This latter lesion may be associated with corrected transposition of the great vessels. Corrected transposition of the great vessels is associated with another interesting mitral valve lesion, referred to as Ebstein's malformation of the left AV valve, in which the left AV valve, which looks like the normal tricuspid valve, is displaced downward into the left ventricle and may be incompetent. Finally, fibroelastosis of the left ventricle may cause mitral regurgitation by sticking the leaflets to the wall of the ventricle and holding the valve open.

Without much difficulty, we can dispose of diagnoses 6 and 7 in Table 1. The mitral lesions associated with the corrected transpositions can be excluded by the electrocardiogram which, in our patient, has definite Q waves in Leads V_5 and V_6. This electrocardiographic pattern is almost never seen with corrected transposition.[2] There were several other points against corrected transpositions. First, when mitral insufficiency occurs in this malformation, it is usually not this severe and clinically dominant, and it is not associated with a giant left atrium. Second, there was no evidence of any of the defects commonly associated with corrected transposition, such as ventricular septal defect and pulmonary stenosis. Fibroelastosis is unlikely because patients with this disease usually die earlier and murmurs are usually not a prominent feature. Murmurs of such intensity are not heard in this disease, and the left atrium, though enlarged, is never this big.

At this point I was left with an isolated congenital mitral insufficiency, which was probably anatomically one of the first five diagnoses in Table 1. In this malformation, the left atrium may be large, there is an early history of failure, growth is retarded, and the electrocardiogram shows left ventricular hypertrophy. There is no certain way of differentiating between the first five types of congenital mitral insufficiency. In Dr. H. B. Taussig's book[3] there is a drawing of a heart exhibiting a kind of mitral insufficiency in which the mitral valve is replaced by a perforated diaphragm. The clinical course in this patient was similar to that of the subject of today's conference. There was auricular fibrillation, a huge left atrium, and an enlarged left ventricle. I thought the patient under discussion today would have a similar mitral valve.

Therefore, in summary, on the basis of the protocol, x-rays, and electrocardiogram before I received the catheterization data, my diagnosis was congenital mitral insufficiency due to a fused fixed perforated diaphragm in place of the mitral valve.

Dr. Eugene Braunwald: A right heart catheterization was carried out and the pressure in the right atrium was markedly elevated with V wave peaks of 17 mm. Hg and a mean pressure of 13 mm. Hg. The catheter crossed an atrial communication into the left atrium where the pressure pulse was found to have V wave peaks of 27 mm. Hg and the mean pressure in the left atrium was 15 mm. Hg, only slightly but distinctly higher than the mean pressure in the right atrium. The contours of the two pressure pulses were also quite different. The systolic pressure in the right ventricle was elevated to 55 mm. Hg; the end-

diastolic pressure was 15 mm. Hg; the femoral arterial oxygen saturation was normal.

The krypton[85] inhalation test[4] for the characterization of left-to-right shunts indicated a value of 46% in the right atrium. The upper limit of normal is 15%, and the value observed in our patient represents a left-to-right shunt entering the right atrium. The value of 34% in the right ventricle confirmed the fact that a left-to-right shunt existed.

Indicator dilution curves were obtained. Injection of indocyanine dye into the left atrium and sampling from the femoral artery resulted in a curve which indicated the presence of a left-to-right shunt. Injection of dye into the inferior vena cava showed no evidence of a right-to-left shunt, but showed a broad diffuse curve which was compatible with congestive heart failure and/or a left-to-right shunt. The levels of pressure in the various cardiac chambers and the results of the krypton[85] test and of the dye dilution curves were then sent to Dr. Ross *after* he had prepared the foregoing discussion. However, we did not indicate how the left atrium was entered.

DR. RICHARD S. ROSS: I should have asked a question when I first got the catheterization data because I have just realized for the first time that the catheter entered the left atrium. I had assumed that the transseptal technic[5] had been employed, and I am distressed to learn that the left atrium was entered without puncture of the septum.

The catheterization report adds four important facts to the list of clinical evidence we have already considered:

1. Evidence of a left-to-right shunt into the right atrium.
2. Right ventricular systolic hypertension.
3. No right-to-left shunt.
4. Tall V waves in the left atrium.

The next step is to consider the clinical diagnosis of congenital mitral insufficiency in the light of the catheterization data. Certainly, the tall V waves support this diagnosis and the right ventricular hypertension was consistent with it. The evidence of the left-to-right shunt into the right atrium was difficult to reconcile with the large left atrium. It is difficult to see how the left atrium could have reached this size if there were an atrial septal defect, as the atrial septal defect would tend to decompress the left atrium. It is well recognized that in Lutembacher's syndrome, in which the hemodynamic situation is similar, though the mitral valve is involved in a different way, the left atrium is not huge.

We have seen three patients who have mitral insufficiency and an ostium secundum defect. These people by and large have not been severely ill, and the left atrium has not been as big as we would have expected it to be on the basis of the mitral valvular disease alone. They have not had signs of gross left ventricular hypertrophy on electrocardiogram or on x-ray. The systolic murmurs were far less impressive than the one heard in this patient.

A similar set of cases has been reported by Bashour and Simmons.[6] None of their cases of mitral insufficiency and ostium secundum atrial septal defects had a left atrium as large as did our patient. Of course, it could be said that in this particular case there was more than the usual amount of mitral insuf-

ficiency and a very small atrial defect, and that this accounted for the unusual clinical picture.

Before settling on this diagnosis, I thought I should consider some other possibilities, so I began to consider the possible sources of a left-to-right shunt of oxygenated blood into the right atrium. The various possibilities are:

1. Aorta to right atrium.
2. Left ventricle to right ventricle—tricuspid insufficiency to right atrium.
3. Left ventricle to right atrium.
4. Left atrium to right atrium.

The simple atrial defect can be excluded because of the size of the left atrium. The aorta to right atrium shunt can be excluded on the basis of physical findings; patients with this communication almost always have a continuous murmur, are usually sicker, and the disease runs a more rapid course. The possibility of the ventricular septal defect with a regurgitant tricuspid valve seemed real, but on the basis of the electrocardiogram, it was excluded. If the right side of the heart were overloaded by a ventricular septal defect and tricuspid insufficiency, there would certainly be evidence of right hypertrophy in the electrocardiogram. The absence of right hypertrophy on the electrocardiogram was also the major objection to the diagnosis of ostium primum defect. The objections were the same as those raised in the earlier discussion.

The diagnosis selected will have to provide an explanation for the following findings:

1. Oxygenated blood to right atrium.
2. Incompetent mitral valve.
3. Huge left atrium (intact atrial septum).
4. Left ventricular hypertrophy.

The large left atrium excluded the existence of a significant atrial septal defect and yet we had evidence of oxygenated blood entering the right atrium. The left ventricular hypertrophy that we saw in the EKG suggested that there might be a cause of ventricular overloading other than the mitral insufficiency.

In a search for other causes of left ventricular hypertrophy, I considered various kinds of aortic stenosis and found an illustration in Dr. Taussig's book[3] which shows an infundibular aortic stenosis with anomalous insertion of the chordae of the mitral valve. This insertion caused the aortic leaflet of the mitral valve to be pulled away from the mural leaflet. The patient died, presumably due to a combination of mitral insufficiency and an infundibular aortic stenosis. This malformation would have explained all the findings in today's case except for the shunt. From this case, I was led to a case reported by Dr. Charlotte Ferencz in 1957 which had all of the features necessary to explain the findings in the case today.

In conclusion, I believe the patient under discussion today had the malformation described by Ferencz. The x-ray findings in this malformation are almost identical with those presented today. The left atrium is equally prominent and gives the same configuration to the right heart border in the PA projection (Figure 4). The other projections show the massive dilatation of the left

atrium and the enlarged left ventricle. The electrocardiogram is also similar to that of today's patient. The tall R waves over the left precordium are accompanied by similar ST segment changes.

The anatomy of the heart in Ferencz' patient can be seen in Figure 5. The chordae from the aortic leaflet of the mitral valve were attached to the ventricular septum and the mitral valve was rendered incompetent. These same anomalous chordae formed a network in the outflow tract of the left ventricle and interfered with left ventricular emptying. There was a communication between the left ventricle and the right atrium which would explain very nicely the left-to-right shunt with an intact atrial septum. Before hearing Dr. Braunwald's discussion of the catheterization I had assumed that the atrial septum was intact, and I still feel it hard to explain the large left atrium in any other way.

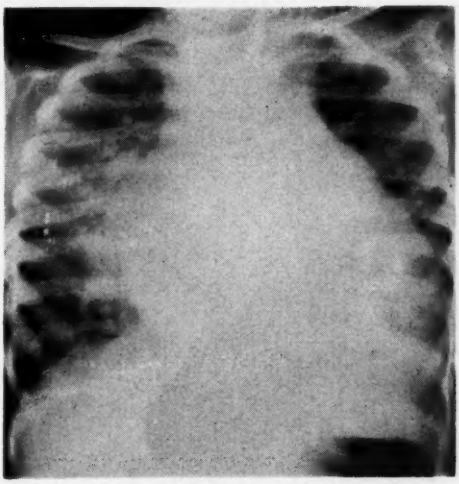


FIG. 4. Chest roentgenogram of patient described by Ferencz.[7] (Reproduced by permission of Bull. Johns Hopkins Hosp. **100**: 209, 1957.)

The diagram in Figure 6 shows how the heart in Ferencz' patient would function. If this isn't the right diagnosis, I'm quite sure that it would give an identical clinical picture. The chordae from the mitral vaive are shown extending across the outflow tract of the left ventricle. There is a communication between the left ventricle and the right atrium. There is a huge left atrium, which of course has many hemodynamic factors operating to make it so large: first, there is an intact septum; second, the mitral valve is incompetent; third, there is left ventricular outflow obstruction so that the pressure in the left ventricle is very high; and fourth, there is a left-to-right shunt so that the return of blood to the left atrium from the lung would be increased.

Therefore, in conclusion, I think the correct diagnosis is left ventriculo-right atrial communication, with mitral insufficiency due to anomalous insertion of the chordae tendineae, and obstruction of left ventricular outflow due to the chordae tendineae extending across the left ventricular outflow tract.

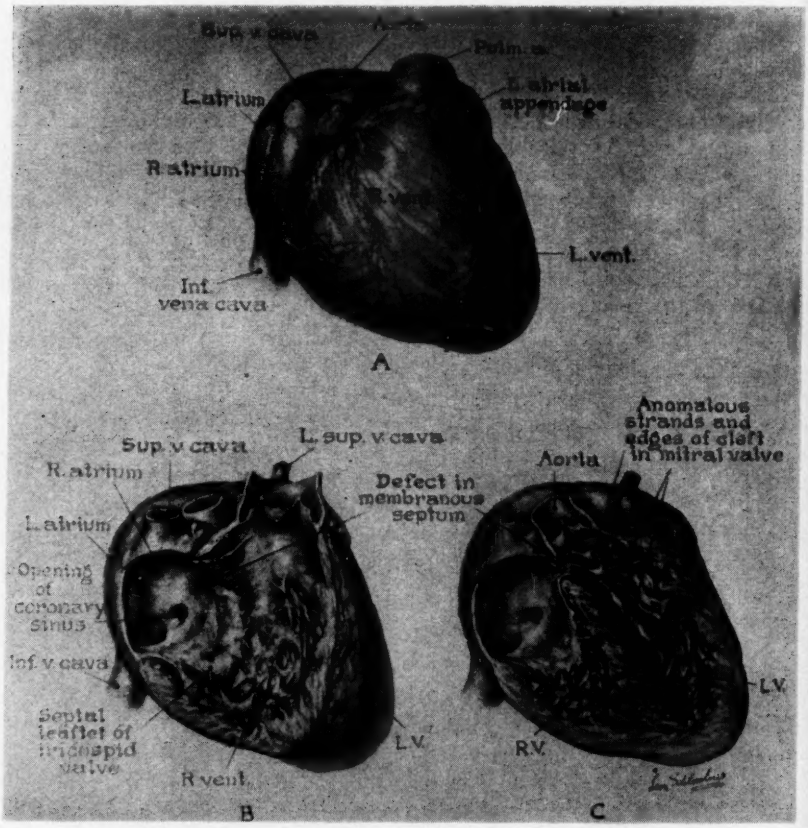


FIG. 5. Drawing of the heart in the case described by Ferencz. (Reproduced by permission of Bull. Johns Hopkins Hosp. **100**: 209, 1957.)

DR. EUGENE BRAUNWALD: Thank you very much for this most instructive discussion, Dr. Ross. In passing the catheter from the right atrium to the left, we didn't assume that it had passed across an atrial septal defect because the left atrium was so large and because there was a distinct pressure difference between the two atria. The possibility was considered that the catheter had been passed across a patent foramen ovale. Dr. Morrow operated upon this patient and I will ask him to describe the operative findings and the clinical course.

DR. ANDREW G. MORROW: I'm glad that we did not have to deal with the type of anomaly reported by Ferencz and which you discussed, Dr. Ross. Before the operation we were not certain of the exact diagnosis, but it seemed clear that mitral regurgitation was the dominant lesion and the one which should receive first consideration. For this reason we made a bilateral anterior thoracotomy so that we might approach any chamber of the heart and would also have optimal exposure of the left atrium.

The entire heart, as you might imagine, was enormous, and the left atrium was particularly prominent. It bulged out behind the right atrium and venae cavae, extending several centimeters beyond the border of the right chambers of the heart. The right atrium was also strikingly enlarged, and there was a faint systolic thrill over it. Over the exposed posterior portion of the left atrium, however, there was an intense systolic thrill.

The digital intracardiac exploration, through the right atrial appendage, was revealing. In the region of the foramen ovale I could feel no interatrial communication but low in the right atrium, immediately above the tricuspid annulus, was a tiny defect which would not admit my finger. Most strikingly, one could feel an intense systolic jet of blood impinging on the interatrial septum from the left side. There was also evidence of a moderate jet of tricuspid regurgitation.

When the cannulations and other preparations for bypass had been completed, I introduced my finger into the left atrium. I could reach the mitral valve only with some difficulty because of the size of the atrium but could easily feel an intense regurgitant jet of blood coming through it. By palpation the jet did not seem to be localized to a commissure but more to the central portion of the valve. We then went on bypass and opened the left atrium from the right side. When the blood had been evacuated we could see a small interatrial

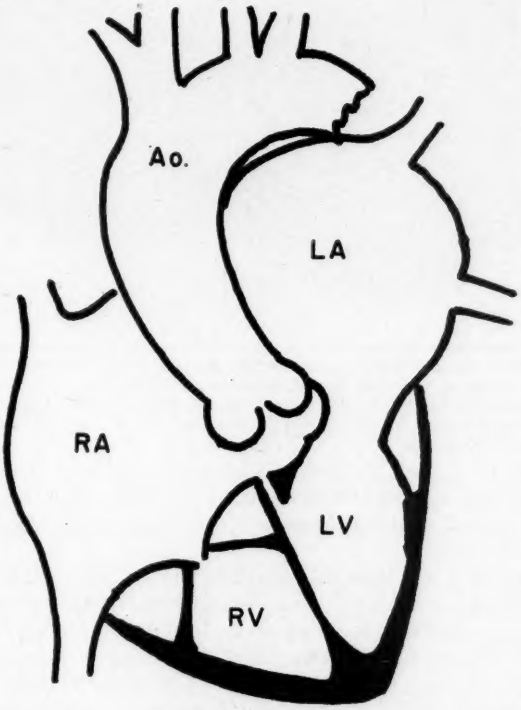


FIG. 6. Diagrammatic representation of the lesion in the case described by Ferencz.

communication which lay immediately above the atrioventricular ring. This was less than a centimeter in diameter. Coming through the opening from the right side was dark blood, the coronary return.

Inspection of the mitral valve revealed that the posterior or mural leaflet was somewhat thickened but was essentially normal. In the anterior or aortic leaflet of the mitral valve, however, there was a complete cleft which extended from the common endocardial cushion through the length of the valve to its free margin. The cleft was of the type typically seen in the partial form of persistent atrioventricular canal. We closed the interatrial septal defect from the left side

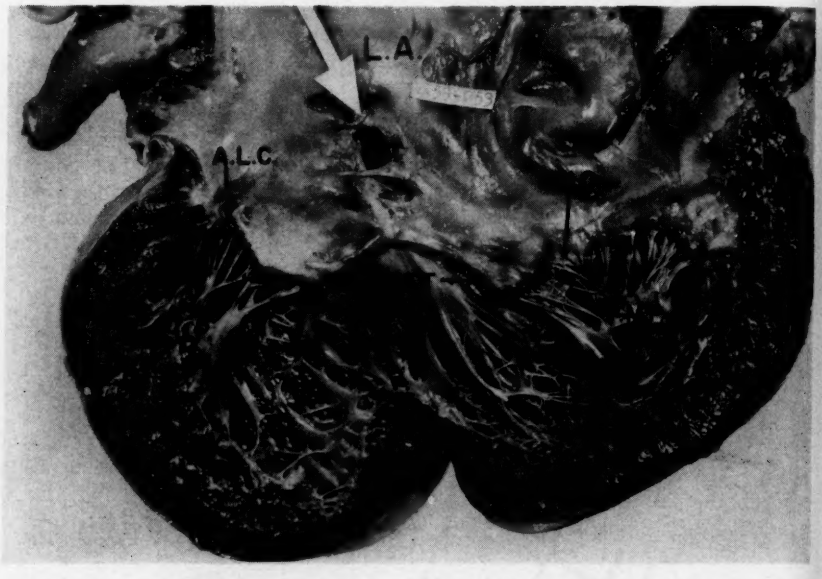


FIG. 7. The left atrium (L.A.), mitral valve, and left ventricle (L.V.) are opened. The left atrium is markedly dilated and the left ventricle is hypertrophied and dilated. The sutures closing the ostium primum defect (white arrow) have been removed. The defect is located at the apex of the cleft in the anterior mitral leaflet. The chordae tendineae extending to the anterolateral (A.L.P.) and posteromedial (P.M.P.) papillary muscles are normal. The anterolateral (A.L.C.) and posteromedial (P.M.C.) commissures are designated for orientation purposes.

with a few sutures and then approximated the valve cleft with a series of reinforced interrupted mattress sutures. After it had been repaired the valve seemed to be competent.

The left atriotomy was then closed and we opened the right atrium in order to inspect the tricuspid valve. There was obvious tricuspid regurgitation, but we could find no discrete lesion that seemed amenable to repair. There was no distinct cleft in any of the leaflets. The regurgitation through the tricuspid valve seemed to be coming from the commissure between the septal and posterior leaflets and it was felt that it might be corrected by an annuloplasty. This was

performed with three or four mattress sutures placed through the annulus at the commissure described.

We then came off bypass and the child maintained his circulation well. There was still enlargement of the left atrium and it was quite tense, but we could not feel systolic thrill in the left atrium after the repair. The child did well during the day of operation and that night. On one occasion his blood pressure fell for no apparent reason, but it responded immediately to a single small dose of metaraminol. On the day following the operation, he was sitting up in bed. The nurse was having him cough to evacuate secretions. He did cough, and vigorously, and that moment he died. The resident was there and immediately



FIG. 8. The mitral valve viewed from the left atrium. The cleft in the anterior mitral leaflet (A.M.L.) is readily apparent. The small defect (white arrow) in the lowest portion of the atrial septum is located at the apex of the cleft. The posterior mitral leaflet (P.M.L.) is unremarkable. The posteromedial (P.M.C.) and the anterolateral (A.L.C.) commissures are evident.

opened the chest; the heart was found to be in arrest and could not be resuscitated.

DR. EUGENE BRAUNWALD: The pathologic findings will now be presented and discussed by Dr. Roberts.

DR. WILLIAM C. ROBERTS: The complete cleavage or cleft in the anterior or aortic leaflet of the mitral valve produced a wide-open canal between the left atrium and the left ventricle (Figures 7, 8). The mitral regurgitation led to extreme dilatation of the left atrium and to moderate hypertrophy and dilatation of the left ventricle. A small defect, measuring only 1 cm. in its largest diameter, was present in the lower portion of the atrial septum—a so-called ostium primum

type atrial septal defect. In addition, the tricuspid valve was abnormal. Although there was no cleavage of its septal leaflet, the most superior portion of the septal leaflet was absent, and the remaining portion of this leaflet was shortened. These abnormalities prevented complete closure of the tricuspid valve during ventricular systole, and tricuspid regurgitation resulted. Other cardiovascular findings included anomalous chordae tendineae from the anterior leaflet of the mitral valve, a quadricuspid pulmonic valve, and moderate hypoplasia of the right coronary artery. The lungs were collapsed bilaterally; the liver and spleen showed marked changes of chronic passive congestion.

The normal mitral valve consists of two leaflets, the anterior, which is the larger and which is continuous with the aortic valve, and the posterior. Nor-

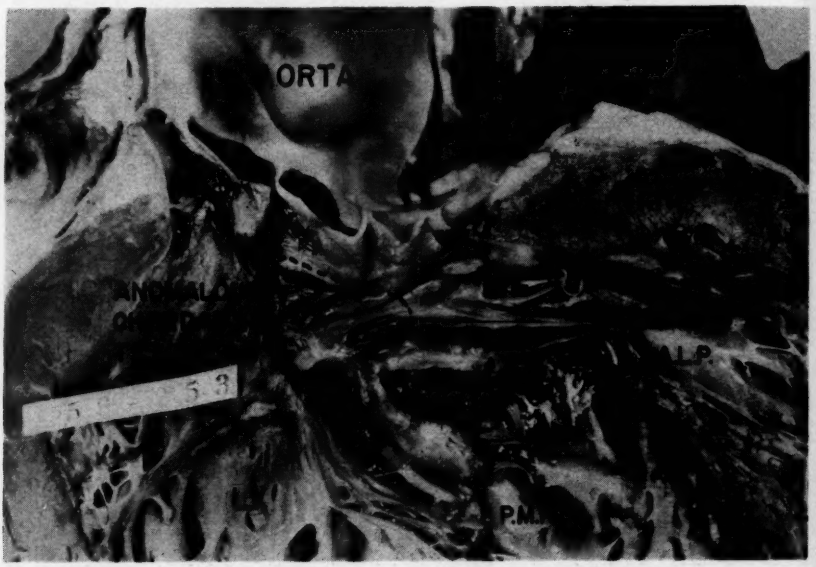


FIG. 9. The left ventricle (L.V.), aortic valve, and aorta are opened. The anomalous chordae tendineae, enclosed by the broken lines, extend from the anterior portion of the cleft anterior mitral leaflet to the crest of the ventricular septum immediately beneath the aortic valve cusps. The anterolateral (A.L.P.) and posteromedial (P.M.P.) papillary muscles are labeled.

mally, chordae tendineae from the margins of each of the two leaflets insert only into the two papillary muscles of the left ventricle. In the patient under discussion the anterior mitral leaflet was divided by the cleft into two halves, which may be designated "anterior" and "posterior." Chordae tendineae not only inserted into the two papillary muscles of the left ventricle, but chordae from the "anterior" portion of the anterior mitral leaflet also inserted into the crest of the muscular ventricular septum immediately beneath the aortic valve (Figure 9). These thickened and fused anomalous chordae, which have no counterpart in the normal heart, are always present when there is a cleft anterior mitral leaflet. They are important because, as emphasized by Edwards,[8] if they are

not divided at the time the cleft is repaired, some mitral insufficiency will invariably remain. Caution must be exerted by the surgeon, however, when cutting these accessory chordae in order not to lacerate an aortic valve cusp or perforate the membranous ventricular septum. In addition, as already stressed by Dr. Ross, these anomalous chordae may interfere with the outflow of blood from the left ventricle and thus produce a form of subaortic stenosis.

A cleft anterior mitral valve and an ostium primum defect, both of which were present in this patient, are two of the components of the complex anomaly

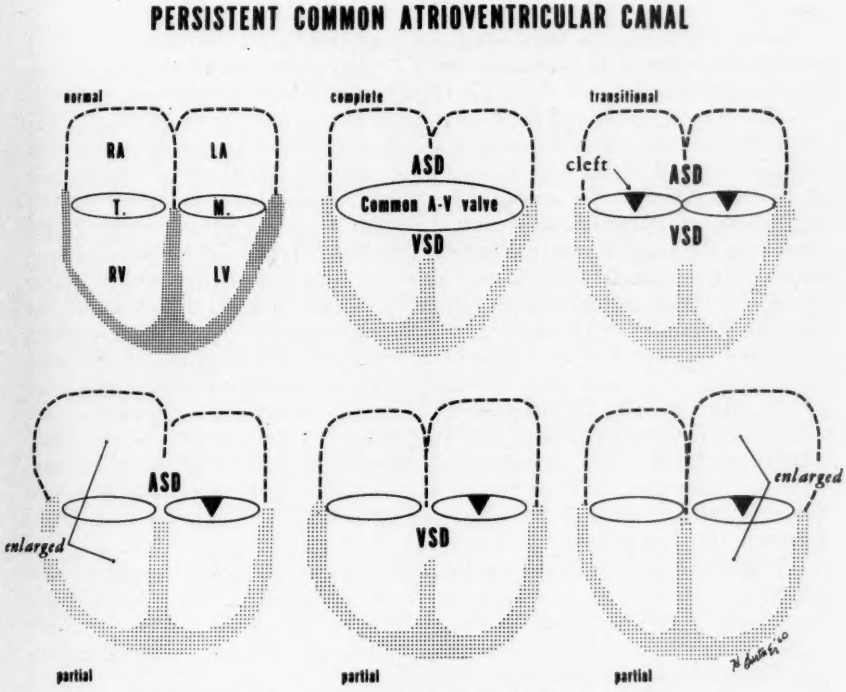


FIG. 10. Diagrammatic representation of various forms of persistent common AV canal. RA, right atrium, LA, left atrium, RV, right ventricle, LV, left ventricle; T, tricuspid valve ring; M, mitral valve ring; ASD, atrial septal defect; VSD, ventricular septal defect.

variously termed persistent common atrioventricular canal, atrioventricularis communis, and endocardial cushion defect. Persistent common atrioventricular canal has been divided by Wakai and Edwards[9,10] into three forms: complete, transitional or intermediate, and partial (Figure 10). In the complete form there is only one valve common to both sides of the heart; an atrial septal defect of the ostium primum type and a high ventricular septal defect are also present. In the transitional form (Figure 10, upper right diagram) the common valve meets in the midline, forming two atrioventricular valves. A cleft is present in the septal leaflet of the tricuspid valve as well as in the anterior leaflet of the

mitral valve. The partial forms (Figure 10, lower diagrams) are characterized by the presence of a cleft in the anterior mitral valve and by the absence of a cleft in the tricuspid valve, although portions of the latter may be shortened or absent.

The patient under discussion had a cleft mitral valve and an atrial septal defect (Figure 10, lower left diagram). Since the atrial septal defect in this patient was extremely small, however, the "run-off" through the defect was likewise small, and consequently (as illustrated in Figure 10, lower right diagram) left atrial dilatation and left ventricular hypertrophy occurred, rather than right atrial and right ventricular enlargement.

In the 109 specimens with congenital malformations of the heart and great vessels in the pathologic collection of the Clinical Center, there are 12 instances of persistent common AV canal (Table 2). The subject of this conference is case 12. The age range of these 12 patients is nine months to 54 years. The partial form of AV canal was the most common. The complete type, the most frequent in most series, was absent. The anterior mitral valve was cleft in all but two patients. In contrast, the septal tricuspid valve was cleft in only one patient and normal in only two. In eight, there was either partial or total absence of the septal leaflet. When the ventricular septal defects were present, they were quite small, except in two patients. The two patients with the large ventricular septal defects had no ostium primum type atrial septal defect, but did have cleft anterior mitral valves. It is not necessary for an ostium primum type atrial septal defect to be present in order that the diagnosis of persistent common atrioventricular canal be made. The one anatomic feature noted in all patients listed in Table 2 is the presence of anomalous chordae tendineae from the mitral valve to the ventricular septum (Figure 9). I therefore consider anomalous chordae tendineae to be a hallmark of the complex anomaly of persistent common atrioventricular canal. Thus, the patient described by Ferencz[7] and discussed by Dr. Ross may perhaps be considered to have had an unusual form of the persistent common atrioventricular canal.

A patent foramen ovale was present in eight of the 12 patients whom we have examined. In three of these eight cases the valve guarding the foramen was incompetent. Of special note is the presence of right ventricular hypertrophy in all patients in this series, except case 12, the patient under discussion, who had isolated left ventricular hypertrophy.

DR. EUGENE BRAUNWALD: The unusual anatomic features presented by this patient and discussed by Drs. Roberts and Morrow were responsible for the clinical and hemodynamic findings which are unusual for patients with the partial form of persistent AV canal. The majority of these patients have a large atrial septal defect and a mild or moderate degree of mitral regurgitation. Clinically, although they present with a loud pansystolic apical murmur they usually have only mild left atrial and left ventricular enlargement. In general the lung fields are plethoric on roentgenograms of the chest and these patients have all of the other clinical features associated with a large left-to-right shunt and increased pulmonary blood flow. The electrocardiograms usually show more marked left axis deviation of the terminal forces than our patient did. In addition, there is evidence of "right ventricular diastolic overload," i.e., an RSR′ configuration in right precordial leads. The absence of this feature in our patient may reasonably

be attributed to the small left-to-right shunt and the only slightly augmented right ventricular output (Figure 1). The prolonged PR interval, which our patient exhibited on several EKGs prior to the development of atrial fibrillation, could have been a clue to the diagnosis since this finding is common in patients with AV canal.

TABLE 2

A Summary of the Anatomic Features in 12 Patients with Persistent Common Atrioventricular Canal Studied at the Clinical Center

Case	Age / Sex, Race	Type	Mitral Valve* (Ant. leaf.)	Tricuspid Valve (Septal leaf.)	VSD	Ostium Primum Defect	Patent Foramen Ovale	Cardiomegaly	Associated Anomalies
1. A54–66	9 mo. / N F	Partial	Cleft	Absent (partial)	+ (minute)	+	+	RVH	0
2. A56–111	17 mo. / W M	Partial	Short	Absent (partial)	+ (minute)	+	+	RVH	0
3. A57–117	26 / W F	Partial	Cleft	Normal	0	+	+ (valv. incomp.)	RVH	0
4. A57–184	14 / W F	Partial	Cleft	Absent (partial)	0	+	+ (valv. incomp.)	RVH	0
5. A57–195	42 / N M	Partial	Cleft	Absent (partial)	0	+	0	RVH	0
6. A57–226	2 / W F	Trans.	Cleft	Cleft	+ (small)	+	+	RVH LVH	Mongolism
7. A59–12	23 / W M	Partial	Cleft	Absent	+ (minute)	+	+ (valv. incomp.)	RVH	Rt. PV→RA† LSCV→CS‡
8. A59–207	54 / W F	Partial	Cleft (partial)	Absent	0	+	+	RVH	CS→LA§
9. A60–41	13 / W F	Partial	Cleft (partial)	Normal	+ (large)	0	+	RVH	0
10. A60–84	13 / W F	Partial	No cleft	Anomalous ¶ chordae	+ (large)	0	0	RVH LVH	LSVC→CS‡ Bicuspid pul. valve
11. A60–276	31 / W F	Partial	Cleft	Absent (partial)	0	+ (small)	0	RVH LVH	0
12. A59–253	14 / N M	Partial	Cleft	Absent (partial)	0	+ (small)	0	LVH	0

*All patients had anomalous chordae tendineae from the mitral valve to the ventricular septum.

†Rt. PV→RA: The right pulmonary veins drained only into the right atrium.

‡LSCV→CS: A left superior vena cava drained into the coronary sinus.

§CS→LA: The coronary sinus drained only into the left atrium. The right atrial ostium of the coronary sinus was atretic.

¶Double orifice, tricuspid valve.

The clinical findings in this patient, and in one other patient with identical anatomic findings, were those of massive mitral regurgitation; there was a prominent apical holosystolic murmur which was transmitted well into the axilla and over the precordium. Prominent left ventricular lifts were palpable. The roentgenographic findings were of left atrial enlargement rather than of increased pulmonary blood flow. Since the atrial septal defect was very small it could

not adequately decompress the left atrium, and a pressure gradient between these two chambers was present throughout the cardiac cycle, particularly during ventricular systole when a large V wave was present in the left atrial pressure pulse; the latter was related to massive mitral regurgitation and is not usually present in patients with mitral regurgitation and a large atrial septal defect.

I shall now ask Dr. Morrow to discuss some of the surgical considerations in persistent AV canal.

DR. ANDREW G. MORROW: From the standpoint of making a decision as to whether a given child or adult with a variety of AV canal should be operated upon, I think that one important consideration is whether the lesion is the complete, the transitional, or the partial form of the anomaly. In other words, if one has to deal only with a cleft anterior leaflet of the mitral valve and to close an interatrial communication, a completely corrective operation can be carried out with an acceptable risk. In a child or a young adult who presents with these findings and no other contraindications we now recommend that operation be undertaken electively, regardless of the presence or absence of symptoms. Our feeling about operation is somewhat less optimistic when the complete form of AV canal is present and there is an associated large interventricular communication. The bundle of His lies immediately under the endocardium, on top of the ventricular septum, and the difficulty in repairing a complete persistent canal is to close the interventricular communication without producing complete heart block. This complication has unfortunately occurred in a large percentage of such patients who were operated upon.

In a patient such as the one described today, i.e., one who presents with the primary problem of mitral regurgitation but in whom a shunt into the right atrium is also present, another problem presents itself. First, it is difficult, I think, to be certain before operation that the patient does not have a small atrial septal defect of the ostium secundum type and a mitral valve which is not congenitally cleft but which has been damaged in another fashion, as by rheumatic fever. The importance of this differential diagnosis is that, in general, a cleft mitral valve can be repaired without undue difficulty and a competent valve can be established. On the other hand, the problem of the treatment of rheumatic mitral regurgitation, at this time in our unenlightenment, remains an extremely difficult one.

I feel that one of the reasons this child died may have been the fact that Edwards, at the time of the operation, had not yet published his article about the abnormal chordae tendineae which are present in AV canal.[8] He points out, on morphologic grounds, that if one does not divide these abnormal chordae, although the anterior leaflet is reconstituted, the chordae may restrict the motion of the valve and hold it down in the left ventricle during ventricular systole. Thus even though the leaflet itself appears competent there still may be significant mitral regurgitation. At the time of the operation we were unaware of the existence or the importance of these structures. Perhaps if we had done a more effective repair the child might have survived.

DR. EUGENE BRAUNWALD: It is technically simpler to close the atrial septal defect than it is to restore complete competency to the mitral valve in patients with the lesion which our patient presented. If this occurs the patient can actually be made worse by operation, since the atrial defect does serve as a

type of escape valve for the distended left atrium. In the other patient with this malformation whom we have encountered, the pulmonary artery pressure prior to operation was 22/8 mm. Hg. Following operation, the defect remained closed but mitral regurgitation persisted, the pulmonary artery pressure rose to 54/20 mm. Hg, and the patient required a second operation.

Dr. Ross, do you have any further comments?

DR. RICHARD S. ROSS: Do you think that the anomalous chordae produced left ventricular outflow obstruction in this case? If they did, and if the mitral valve were repaired but the left ventricular outflow obstruction were allowed to remain, a satisfactory result could not be anticipated.

DR. EUGENE BRAUNWALD: At the time of the left ventricular catheterization there was no gradient between the left ventricle and the aorta; therefore there is little hemodynamic evidence that the chordae interfered with left ventricular ejection.

DR. RICHARD S. ROSS: I see. I think I erred in making the categorical assumption that the atrial septum might be intact to explain the giant left atrium. In general this is true, but, as has been pointed out, the atrial size is more a function of the ratio of the magnitude of mitral regurgitation to the size of the atrial septal defect. If there is a lot of mitral regurgitation and a small atrial septal defect, there can be a large left atrium.

QUESTION: How can one differentiate preoperatively the lesion which this patient presented from that described by Dr. Ferencz?

DR. EUGENE BRAUNWALD: Since we have not encountered the latter anomaly I can only speculate: (1) A selective left ventricular angiocardiogram or preferably a selective cine-angiogram with left ventricular injection would show immediate opacification of both atria, while this type of study in our patient would show left atrial opacification prior to right atrial opacification. The value of selective left ventricular angiocardiography in the differential diagnosis of the various forms of persistent common AV canal and of related anomalies has recently been discussed elsewhere in detail.[11] (2) The anomalous chordae in Ferencz' patient presumably resulted in a pressure gradient between the left ventricle and the aorta. This did not occur in our patient. (3) A cardiac catheter could be passed from the right to the left atrium in our patient, but this would not be possible in Ferencz' patient, who had an intact interatrial septum.

QUESTION: What was the cause of the diastolic rumbling murmur at the apex? There was no evidence of mitral stenosis at autopsy.

DR. EUGENE BRAUNWALD: In patients with pure mitral regurgitation of large degree a diastolic rumbling murmur is frequently audible at the apex. This is related to the flow of abnormally large volumes of blood from the left atrium to the left ventricle during diastole.

SUMMARIO IN INTERLINGUA

Le patiente esseva un puero de 13 annos de etate in qui—al etate de sex annos, durante le curso de un maladia febril—un forte murmure systolic apical e cardiomegalia habeva essite constatate. In le curso del sequente annos, ille esseva hospitalisate repetitemente a causa de congestive disfallimento cardiac. Le examine physic monstrava pulsante venas in le collo, un allargate hepate, e un forte e findite secunde sono cardiac in le area pulmonal. Forte murmures systolic e diastolic esseva

audibile al apice. Le electrocardiogramma revelava fibrillation atrial e deviation axial al sinistra. Le catheterismo cardiac monstrava hypertension systolic dextero-ventricular, un micre derivation sinistro-dextere que entrava in le atrio dextere, alte undas V in le pulso de pression sinistro-atrial, e un distincte gradiente de pression inter le duo atrios. Le diagnose differential inter iste lesion e regurgitation mitral in le pueritia es discutite in detalio.

Al operation il esseva trovate que le patiente habeva un micre defecto atrio-septal del typo de atrio prime e un complete scission in le lobo anterior del valvula mitral. Le duo lesiones esseva reparate, sed le patiente moriva le die post le operation.

Es discutite le aspectos anatomic, pathologic, e clinic de persistente canal atrio-ventricular.

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CASE REPORTS

CARCINOMA OF THE LUNG ASSOCIATED WITH MARKED ADRENOCORTICAL HYPERPLASIA AND ADRENAL HYPER-RESPONSIVENESS TO ACTH IN THE ABSENCE OF CUSHING'S SYNDROME*

By Leon J. Marks, M.D., Albert E. Anderson, M.D., and Harvey Liberman, M.D., *Boston, Massachusetts*

The role of pituitary corticotropin in the regulation of the adrenal secretion of cortisol during the basal state, as well as during periods of stress, has been well documented.[1] The work of several investigators has suggested the existence of a pituitary factor which is separate from conventional ACTH and which primarily affects adrenal growth and weight maintenance without causing the secretion of adrenal hormones.[2, 3] Although Jailer et al.[4] have demonstrated the presence of an adrenal weight-maintaining substance in patients with Cushing's disease due to bilateral adrenal hyperplasia by assaying their plasma in hypophysectomized rats, the clinical significance of a human adrenal growth factor thus far has remained uncertain. The purpose of this paper is to report the case of a patient with carcinoma of the lung who, while alive, had a markedly exaggerated adrenocortical response to conventional ACTH in the complete absence of clinical evidence of Cushing's snydrome and who, at autopsy, had extremely large adrenal glands with adrenocortical hyperplasia.

Case Report

J. M., a 64-year-old white male, entered the Boston Veterans Administration Hospital July 8, 1959, with the chief complaint of a persistent cough of four months' duration. He had lost 10 pounds within the previous six months. Significant physical findings included blood pressure of 110/80 mm. Hg, bilateral Herberden's nodes on the distal interphalangeal joints of the fingers, impaired hearing bilaterally, and dullness to percussion and diminished breath sounds over the left upper chest.

The hematologic data were as follows: hemoglobin, 14.3 gm.%; hematocrit, 45%; white cells, 10,600/cu. mm.; differential count: stab forms, 7%; segmented forms, 63%; lymphocytes, 28%; eosinophils, 2%. Corrected sedimentation rate was 33 mm./hr. Urine examination was normal. Blood chemical findings were: nonprotein nitrogen, 28 mg.%; fasting blood sugar, 81 mg.% Roentgenograms of the chest revealed bilateral emphysema and nodular consolidation of the left upper lobe. An electrocardiogram was within normal limits.

At exploratory thoracotomy on August 4, 1959, a carcinoma of the superior segment of the left upper lobe was observed to extend to the left parietal pleura. A

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left pneumonectomy was performed, the patient tolerating the operative procedure without incident. Two weeks postoperatively, a total tumor dose of 3,430 roentgens was administered to the left parietal pleura over a 16-day period, following which the patient was discharged.

The patient was readmitted on December 22, 1959, because of left chest pain and dyspnea of five days' duration. He had lost six pounds since his operation. Physical examination revealed the presence of an effusion in the left hemithorax. A thoracocentesis was performed and 250 ml. of cloudy yellow sterile fluid were removed. A cell block of this fluid was positive for malignant cells. The patient improved on supportive therapy and was discharged to a nursing home.

He was readmitted on January 21, 1960 because of persistent left chest pain and weakness. It was evident on physical examination that fluid had reaccumulated in the left hemithorax. His blood pressure was 105/76 mm. Hg. The hematologic data were as follows: hemoglobin, 13.1 gm.%; hematocrit, 41%; white cells, 13,800/cu. mm.; differential count: stab forms, 11%; segmented forms, 76%; lymphocytes, 12%; eosinophils, 1%. An eosinophil count was 102/cu. mm. Blood chemical values were: urea nitrogen, 12 mg.%; fasting blood sugar, 89 mg.%; total bilirubin, 0.6 mg.%; cephalin flocculation, 2-plus; thymol turbidity, 3.4 U.; total protein, 4.4 gm.%; albumin, 3.1 gm.%; globulin, 1.3 gm%. Serum electrolytes were: sodium, 139 mEq./L.; potassium, 4.2 mEq./L.; carbon dioxide, 29 mEq./L.; and chloride, 100 mEq./L.

TABLE 1

Effect of ACTH Infusion on Free and Conjugated Plasma 17-OHCS Levels of Normal Subjects

Type of Plasma Steroid	Plasma 17-OHCS (μg./100 ml.) Control	6 Hours*
Free	18.4 ± 2.1†	46.1 ± 3.6
Conjugated	14.9 ± 1.8	30.7 ± 2.9

* All patients received a six-hour infusion of ACTH.
† Standard errors of the means are shown.

On January 26, 1960, the adrenal cortical capacity to respond to a six-hour infusion of 30 USP units of ACTH was tested. Blood samples were obtained before and at the end of the infusion for plasma 17-hydroxycorticosteroid (17-OHCS) determinations. Plasma free 17-OHCS were measured by the method of Nelson and Samuels.[5] Plasma conjugated 17-OHCS were analyzed by the method of Bongiovanni and Eberlein.[6] The mean values and the standard error of the mean of free and conjugated plasma 17-OHCS of 15 normal subjects both before and after ACTH infusion are presented in Table 1.

The control free and conjugated plasma 17-OHCS levels of the patient were 18 μg.% and 7 μg.%, respectively. Following ACTH administration, free and conjugated plasma 17-OHCS values rose to 93 μg.% and 42 μg.%, respectively (Figure 1).

Three days following the completion of the ACTH test, the patient developed bronchopneumonia in his right lung and died within 36 hours.

Pathologic Findings: The surgical specimen of the left lung revealed the presence of a carcinoma which arose in the superior bronchus of the left upper lobe. Tumor was present in several of the hilar lymph nodes resected at operation. On microscopic examination the tumor was a grade 2 epidermoid carcinoma.

The significant pathologic processes at post-mortem examination were confined to the thorax and to the adrenals. A moderate amount of cloudy yellow

fluid was found in both pleural cavities from which alpha and beta streptococci were cultured. Diffuse bronchopneumonia was present in the right lung. Tumor was observed in the resected margin of the left lung, the main bronchus of the right lung, the left pleura, the posterior mediastinal, periaortic, and right hilar lymph nodes, and in the bodies of the seventh and eighth thoracic vertebrae. There was a moderate degree of coronary arteriosclerosis. The central venous system was not examined.

Both adrenal glands were greatly enlarged and after careful removal of periadrenal fat, the right adrenal weighed 21 gm. and the left adrenal weighed 33 gm. The cortices of both adrenals were thickened and measured from

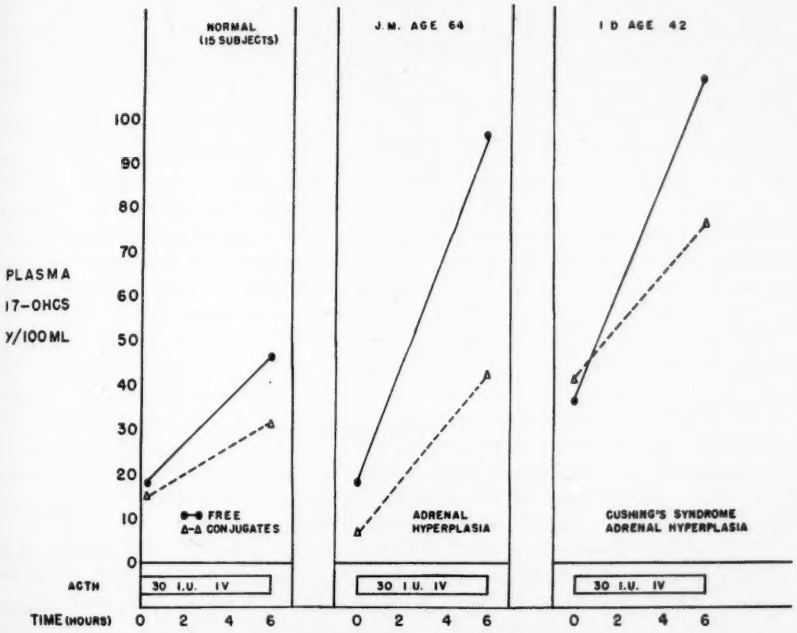


FIG. 1. Comparative responses of free and conjugated plasma 17-OHCS levels to ACTH in normals (mean of 15 subjects), in Patient J. M. (the subject of this report), and in another patient, I. D., who had active Cushing's syndrome.

0.4 to 0.7 cm. The external surfaces were corrugated with a suggestion of nodule formation. On cut section, bright yellow radial streaking was seen in a brown cortical parenchyma. The medullae of both adrenals were a waxy gray and of average size.

Microscopic examination revealed marked bilateral adrenocortical hyperplasia, involving all three zones of the cortex. There was considerable hypertrophy of the cells of the zona glomerulosa and fasciculata. Multiple nodule formation could be seen within the fasciculata. An occasional nucleus of the cells of the fasciculata was enlarged and hyperchromatic. Focal lipid depletion was present in the zona fasciculata and reticularis.

Discussion

The marked adrenocortical hyperplasia observed in our patient at autopsy was in striking contrast to the complete absence of clinical signs suggestive of adrenal hyperfunction during the seven months of careful clinical observation prior to his death. The demonstration of normal control values of both free and conjugated plasma 17-hydroxycorticosteroids are in agreement with the patient's clinical state.

In Figure 1 may be seen both the free and conjugated plasma 17-OHCS response to a six-hour infusion of ACTH in a group of 15 normal subjects, in our patient, J. M., and in a 42-year-old male, I. D., with full-blown Cushing's syndrome. Although the control pre-ACTH free and conjugated plasma 17-OHCS values in patient I. D. are considerably higher than those of patient J. M., the increment rises both in free and conjugated plasma 17-OHCS in response to ACTH are indentical in both patients and are significantly greater than those observed in normal subjects.

An exaggerated free plasma 17-OHCS response to ACTH has been demonstrated by Sandberg et al. in moribund patients,[7] whose pre-ACTH plasma 17-OHCS levels were elevated. This observation was confirmed by Christy et al.,[8] who suggested that the elevated resting and post-ACTH free plasma 17-OHCS values seen in severely ill patients were due in part to the delayed disappearance of cortisol from plasma. They commented that two of their patients with a hyper-response to ACTH had adrenal glands which were normal in weight and morphology at post-mortem examination.

We should like to emphasize that our patient J. M. should not be placed in the foregoing category for the following reasons. First, on the day the ACTH test was performed, he was not critically ill and was being considered for discharge to a nursing home. Second, his resting pre-ACTH free and conjugated plasma levels were not elevated. Third, the marked increase of his conjugated plasma 17-OHCS in response to ACTH is evidence against the thesis that the high value of free plasma 17-OHCS observed after ACTH was due primarily to impaired metabolism of circulating cortisol.

The authors favor the concept that the adrenal glands of the patient were exposed to unidentified growth factor over a long period of time. The primary action of this X substance was to increase the size of the adrenal cortex without affecting the adrenal secretion of corticosteroids. If one assumes that these large adrenals remained responsive to conventional ACTH during their growth, then endogenous ACTH secretion must have diminished as adrenal hyperplasia developed. If pituitary ACTH secretion did not decrease, then the adrenal output of cortisol should have risen and Cushing's syndrome would have appeared. Indeed Cushing's syndrome has been reported in a few patients dying with oat-cell carcinoma of the lung who had bilateral adrenal cortical hyperplasia at autopsy.[9, 10]

Adrenal weight-maintaining effects have been found in growth hormone fractions by Reinhardt, Geschwind, and Li,[11] by Young,[12] and by Cater and Stack-Dunne.[3] Jailer et al. observed that plasma from two patients with "active acromegaly" possessed significant adrenal weight-maintaining activity in hypophysectomized rats.[4] Although patients with acromegaly may have enlarged adrenal glands at autopsy,[13] acromegalic patients have not been observed

to have an exaggerated plasma 17-OHCS response to ACTH.[4] Liddle et al.[14] administered a highly purified beef growth hormone preparation to two patients for five successive days and did not observe any change in adrenocortical responsiveness to conventional ACTH.

Thus, at the present time it appears that the chemical identity of any specific adrenal growth hormone in man remains unresolved. It is our hope that the reporting of the present case in detail will stimulate further investigation in this complex field.

Summary

A case is reported of epidermoid carcinoma of the lung associated with extreme bilateral adrenocortical hyperplasia. Although this patient exhibited a markedly exaggerated free and conjugated plasma 17-hydroxycorticosteroid response to conventional ACTH, no objective evidence of either hyper- or hypoadrenocorticism was present during his entire clinical course. It is postulated that these large adrenals were due to the action of an unidentified adrenal growth factor, which did not affect adrenocortical secretion.

Summario in Interlingua

Es reportate un caso de carcinoma epidermoide del pulmon, associate con extreme hyperplasia adrenocortical bilateral. Ben que iste patiente exhibiva un marcatemente exaggerate responsa del libere e del conjugate 17-hydroxycorticosteroides del plasma a ACTH conventional, nulle signo objective de hyper- o hypoadrenocorticismo esseva presente durante su integre curso clinic. Es postulate que iste grande adrenales esseva causate per le action de un non identificate factor de crescentia adrenal que non afficeva le secretion adrenocortical.

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FUNCTIONING MALIGNANT BRONCHIAL CARCINOID WITH CUSHING'S SYNDROME AND RECURRENT SINUS ARREST*

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For many years bronchial carcinoid, a type of bronchial adenoma, was considered not to be potentially malignant. In 1937, however, Zamora and Schuster[1] mentioned the first case of metastasis from a bronchial adenoma. A correlation between malignant carcinoid tumors of the small intestine and a bizarre syndrome, subsequently called "carcinoid syndrome," was emphasized by Thorson et al.[2] in 1954.

In 1956 MacDonald[3] reviewed 57 cases of carcinoid syndrome with the primary tumor in the gastrointestinal tract. In the same year, Mattingly[4] in a thorough review of the literature described the functioning carcinoid tumor. Through 1959 a total of at least 65 cases of the carcinoid syndrome was noted in our review of the literature. A report of the carcinoid syndrome in a patient with bronchial carcinoid was first described in 1958.[5] Subsequent reports of its occurrence have been noted on several occasions since that time.[6-11]

The interesting report of Kovach and Kyle[12] summarized seven cases of Cushing's syndrome associated with bronchogenic carcinoma. It is believed that a further clinical potential of the malignant bronchial adenoma in association with Cushing's syndrome has been demonstrated for the first time by the following case report.

Case Report

First Admission: On November 30, 1955, a 35-year-old white male bricklayer was admitted to the Veterans Administration Hospital, Long Beach, California, complaining of a cough which was nonproductive and paroxysmal since 1952, accompanied by frequent fainting spells since 1954. Admission x-ray showed a round mass in the upper portion of the left hilum which had not been present on a chest x-ray in 1951. Bronchoscopy showed a smooth, slightly injected mass obstructing the left

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upper lobe bronchus. Biopsy of this mass showed no evidence of tumor. On December 20, 1955, a left thoracotomy was performed and a tumor extending from the hilum to the upper lobe of the left lung was found. Microscopic examination of an adjacent lymph node showed "anaplastic carcinoma" in a crushed specimen. When the pericardial sac was opened, tumor was seen extending along the pulmonary artery and vein into the pericardial space. Consequently, no resection was done. From January 12, 1956 to February 3, 1956 the patient received deep irradiation therapy to the left hilar area.

Second Admission: On June 20, 1957 the chief complaint was the increasing severity and frequency of sudden episodes of unconsciousness lasting from several seconds to several minutes. These were not associated with any aura or postictal phenomena. Unconsciousness could not be reproduced by pressure on either carotid sinus.

The patient received eight electroshock treatments for anxiety and depression. These were discontinued because of frequent episodes of convulsions which at that time were considered to be the result of cerebral metastases. Blood pressure varied from zero during a seizure to the resting normal of 120/70 mm. Hg. The frequency, duration, and intensity of the seizures became quite variable and were not controlled by many medications, including atropine, gr. 1/37 every four hours, isoproterenol hydrochloride (Isuprel) glossets, 20 mg. every four hours, and on an empirical basis, medroxyprogestrone acetate (Pro-vera) 10 mg. three times daily.

Several tender, hard, discrete, cutaneous nodules of variable size were noted on March 26, 1958. These became larger and subsequently were palpated over all parts of the body except the hands, feet, face, and scalp. In September, 1958, a moderately deep cyanotic flush, rather constant in intensity, was noted on the face and especially around the ears and lateral aspect of the neck. This persisted throughout hospitalization. The liver was never palpable. A grade 1 pulmonic systolic murmur, transmitted to the left supraclavicular area, progressively increased to grade 3. A painful, slowly enlarging nodule in the lower pole of the left testicle, first noted in January 1958, was removed by orchiectomy October 22, 1958. Microscopic examination showed malignant carcinoid. Comparison with subsequent biopsies of cutaneous nodules and with the original hilar lymph node biopsy, secured in 1955, revealed that all lesions were maligant carcinoid. Microscopic examination for carcinoid of the appendix excised in 1946 showed only "acute appendicitis." The 5-hydroxyindoleacetic acid (5-HIAA) excretion in the urine was 27 mg./24 hr. compared with the normal of 2 to 8 mg./24 hr., indicating a functioning carcinoid. Numerous electrocardiograms were normal; however, one taken on November 7, 1958, during a typical seizure, showed sinus arrest and asystole (Figure 1). Thus, it was demonstrated that these seizures were due to recurrent sinus arrest and asystole, presumably due to involvement of the heart and adjacent structures by carcinoid tumor.

Beginning January 13, 1959, the patient developed recurrent furunculosis. Severe, intermittent, left anterior flank pain, accompanied by albuminuria for the first time, began March 10, 1959. Subsequently, on several occasions, his urine contained calculi in the form of hydroxyl apatite ($Ca_{10}[PO_4]6[OH]_2$). In July, 1959, moon facies developed and subsequently buffalo hump, mild kyphosis, worsening furunculosis, glycosuria, hyperglycemia, and hypertension. No striae were seen. The 24-hour urinary excretion of 17-ketosteroids was 34 mg.; a similar determination for 17-ketogenic steroids was 41.8 mg. These findings indicated that the patient had Cushing's syndrome. During this time the seizures became strikingly milder and less frequent, in spite of the fact that no preventive medication was given. After adrenal suppression and stimulation tests, the patient developed 2-plus edema of the hands and feet. His condition progressively deteriorated and he died November 4, 1959.

General Laboratory Data: Several electroencephalograms showed neither discrete lesions nor evidence of convulsive disorder. Several spinal fluid examinations were negative for tumor cells and showed an increase in protein ranging from 45 mg.% to 61 mg.%; chlorides were 700 mg.% on one occasion. Repeated red and white blood cell counts, serum electrolytes, and liver profile studies were normal. Single determinations for the following tests were negative: Friedman's test, urea clearance, urinary prolan A. Beginning March, 1958, numerous determinations of the specific gravity of urine, alkaline in reaction, varied between 1.003 and 1.010; previously the specific gravity ranged between 1.014 and 1.024, acid in reaction. The 24-hour volume of urine varied between 4,500 ml. and 6,400 ml. X-rays of the pelvis, spine,

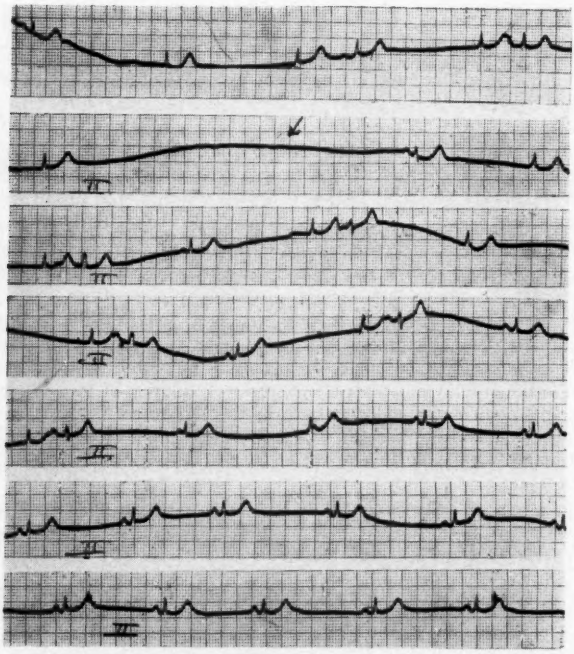


FIG. 1. Electrocardiogram taken during a typical seizure shows sinus arrest and asystole.

skull, and hands on several occasions were negative. A flat plate of the abdomen, intravenous pyelogram, sigmoidoscopic examination, barium enema, and x-ray studies of the upper gastrointestinal tract and small bowel were negative. A gall-bladder dye series showed nonvisualization. Tests for occult blood in the stools were negative.

Laboratory and Clinical Data Concerning Functioning Carcinoid (Beginning October 24, 1958): Twenty-four-hour urinary excretion determinations of 5 hydroxyindoleacetic acid ranged from 13 to 27 mg. (normal 2 to 8 mg.).[13] A 24-hour collection of urine, following administration of 2.5 mg. reserpine intramuscularly, revealed 37 mg. of 5-hydroxyindoleacetic acid, the highest obtained in this patient. After intravenous injection of 0.055 mg. of histamine diphosphate base, the 24-hour

urinary excretion of 5-hydroxyindoleacetic acid was 27 mg. Twenty milligrams of serotonin creatinine sulphate,* given orally for three days, showed a change in eight-hour urinary 5-hydroxyindoleacetic acid excretion from controls of 0.7 mg. and 0.8 mg./8 hr. to 7.3 mg., 9.6 mg., and 15.7 mg./8 hr. on the three succeeding days. The amino acid oxidase inhibitor, beta phenylisopropyl hydrazine hydrochloride (Catron), given orally, 3 gm. four times daily for four days, produced no significant change from the 24-hour control excretion of 28.2 mg. of 5-hydroxyindoleacetic acid. The highest control blood pressure of 120/100 mm. Hg was elevated to a high of 180/122 mm. Hg. Twenty-five milligrams of DL-5-hydroxytryptophan (serotonin precursor) dissolved in 300 ml. of normal saline, given intravenously over a period of one hour, showed no significant change in the urinary excretion of 5-hydroxyindoleacetic acid/8 hr. on the day of administration and on the following day. No variations in skin color, or clinical changes, were noticed with administration of any of the above substances. An analysis of a cutaneous nodule showed serotonin content of 21 μg./gm. of tissue, a mild, although significant increase (normal 1 μg. or less per gram). Thus, the serotonin content was consistent with the diagnosis of functioning carcinoid.[14] However, no excess of serotonin was detected in the blood serum on several occasions. Chromatography of an acetone extract of urine failed to reveal tryptophan or hydroxytryptophan or any other compound which reacted with Ehrlich's reagent to give a blue color. Electrophoretic analysis of the serum showed no abnormalities; protein in the urine concentrated insufficiently for analysis. Serotonin creatinine sulphate (1:2,000) given intradermally showed no altered reactivity of the skin.[15] The ingestion of one ounce of 84-proof brandy produced no skin changes. The highest specific gravity obtained on the Fishberg concentration test was 1.015. Two phenolsulfonphthalein tests showed 10% and 20% excretion of dye respectively in 15 minutes. The urea clearance test was normal. In March, 1959, the Sulkowitch test on random specimens of urine showed a moderate increase in calcium excretion. The excretion of calcium per 24 hours on a low calcium diet was 19.3 mEq./L. (normal 18 mEq./L.); the 24-hour excretion of phosphorus was 0.6 gm. (normal 1 to 2 gm.); the 24-hour excretion of uric acid was 1.15 gm. (normal 0.4 to 0.8 gm.). The hypertonic saline infusion test[16] for the functional integrity of the supraoptico-hypophysial system was normal.

Laboratory and Clinical Data Concerning Cushing's Syndrome (Beginning August 28, 1959): White blood cell count, 17,100/cu. mm.: neutrophils, 88%, lymphocytes, 8%, monocytes, 1%, eosinophils, 1%; hemoglobin, 12.8 gm.%; hematocrit, 38%; direct eosinophil count, 124/cu. mm. (normal, 150 to 250/cu. mm.); blood urea nitrogen, 17 mg.%; fasting blood glucose, 213 mg.%; postprandial blood glucose, 276 mg.%. Determinations on serum were: albumin, 3.7 gm.%; globulin, 1.9 gm.%; sodium, 133 mEq./L.; potassium, 2.1 to 3.3 mEq./L.; carbon dioxide combining power, 35 mEq./L.; chlorides, 78 mEq./L.; calcium, 4.8 mEq./L.; phosphorus, 2.9 mEq./L.

The results of the adrenal suppression test (fludrocortisone acetate, given as Florinef acetate 0.5 mg. orally, twice daily for four days), and four days later the adrenal stimulation test (ACTH-gel, 40 mg., intramuscularly, every eight hours for succeeding four days), were consistent with adrenal hyperplasia (Table 1).

Essential Autopsy Findings: Gross examination. The patient had a moon face and a prominent dorsal fat pad. Several hemorrhagic tumor nodules, measuring up to 2 cm. in diameter, were present in the skin of the trunk and abdomen. There were old left thoracotomy and right lower quadrant scars.

A large hemorrhagic, grayish-white, granular tumor mass measuring 4 by 3 cm. surrounded and partially occluded the main bronchus of the upper lobe of the left lung, extending into the lung parenchyma (Figure 2). The bronchial mucosa was

* Supplied by Vismara Terapeutici, Como, Italy.

TABLE 1

Adrenal Suppression and Stimulation Tests

	17-Ketosteroids in mg./24 hr.	17-Ketogenic Steroids in mg./24 hr.
Adrenal Suppression Test		
Control	45.6 (normal 10 to 22)	32.6 (normal 10 to 20)
Fourth day suppression	50	11
Adrenal Stimulation Test		
Third day stimulation	56	47
Fourth day stimulation	59	117

granular and free from obvious tumor. Tumor surrounded and compressed the left pulmonary artery. Tumor was present in the peritracheal and peribronchial lymph nodes. The bulk of the left lung was collapsed. Fibrous adhesions bound the left pleura to the chest wall and encased the pericardium. The right lung was edematous and congested.

The heart was normal in configuration and size, weighing 300 gm. The valves were intact and free from thickening; the chambers were moderately dilated, especially the right side. Numerous tumor nodules, measuring up to 1.5 cm. in diameter, were scattered throughout the myocardium. These involved the bases of the lateral wall of the right ventricle and auricle, the base of the interventricular septum (Figure 3), and the apex of the posterior wall of the left ventricle. The coronary ostia and lumina were patent and the intima of the arteries was free from sclerosis.

The liver was enlarged, weighing 1,950 gm., was free from tumor, and it revealed marked chronic passive congestion. The spleen was normal in configuration and size, weighing 100 gm. The pancreas, which was enlarged, weighed 200 gm. and contained several small scattered nodules.

The left kidney was enlarged, weighing 200 gm., and it communicated with a large perinephric abscess. Much of the parenchyma was destroyed by purulent necrosis which communicated with destroyed calyces filled with purulent material. The ureter was dilated and contained several large calculi, measuring up to 2 cm. in diameter. The right kidney was enlarged, weighing 150 gm.; it revealed tubular

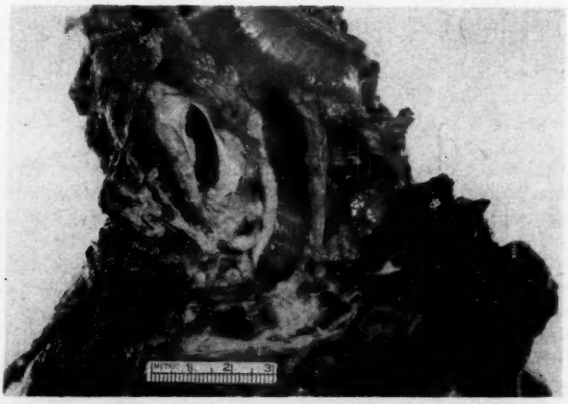


FIG. 2. Tumor constricts the main bronchus of the left upper lobe and the left pulmonary artery.

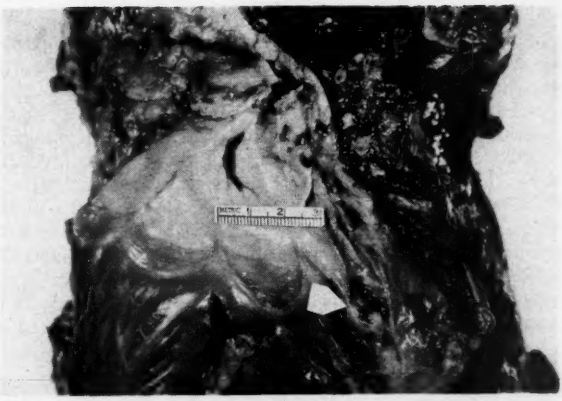


FIG. 3. Pulmonary valve shows no thickening. Arrow points to tumor nodule in base of interventricular septum.

degeneration and focal areas of acute inflammation. The urinary bladder was dilated.

The adrenal glands were enlarged, the right weighing 53 gm. and the left, 44 gm. On cut sections much of the parenchyma of each gland was replaced by hemorrhagic tumor. The remaining parenchyma revealed hyperplasia of the cortex, mainly of the zona fasciculata.

The appendix had been surgically excised. Two polypoid carcinoid tumors were present in the duodenum and two in the ileum; each measured up to 1.5 cm. in diameter. The tumors were confined to the mucosa and submucosa and failed to penetrate the muscularis or serosa (Figure 4). Several small inguinal and mesenteric

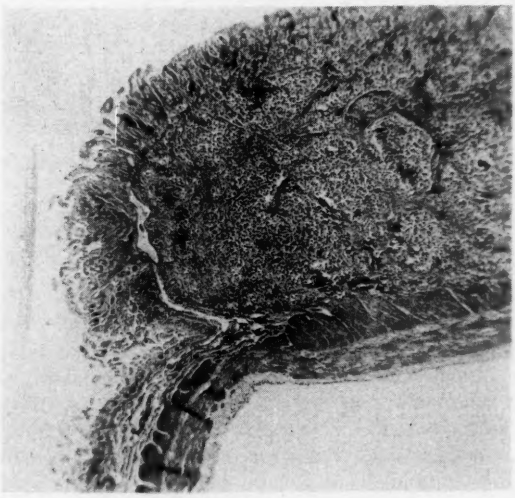


FIG. 4. Polypoid carcinoid of ileum. Tumor confined to mucosa and submucosa. Hematoxylin and eosin stain; × 35.

lymph nodes contained tumor. There were several small tumor nodules in the cortex of the brain. The pituitary was negative for tumor and hyperplasia, although several Crooke's cells were seen on histologic examination.

Microscopic Examination. Microscopically the tumor consisted of solid sheets and cords of mainly uniform, oval, and polygonal cells, having small oval nuclei, occasionally multinuclei, and fairly abundant pink cytoplasm (Figure 5). Thin, vascularized, fibrous septae surrounded groups of tumor cells, producing an acinar pattern. In areas, broad bands of fibrous tissue separated and were infiltrated by tumor nests. Frequently, the tumor cells were anaplastic, varying in size and shape. The tumor was markedly hemorrhagic, and in the lungs it encircled and partially destroyed bronchial cartilage and intermingled with bronchial glands. The bronchial epithelium was destroyed. Tumor invaded vascular and perineural lymphatic channels. Argentaffin stains were negative for granules, and reactions to periodic acid-Schiff (PAS) stains were negative. Tumor metastases were observed in hilar lymph

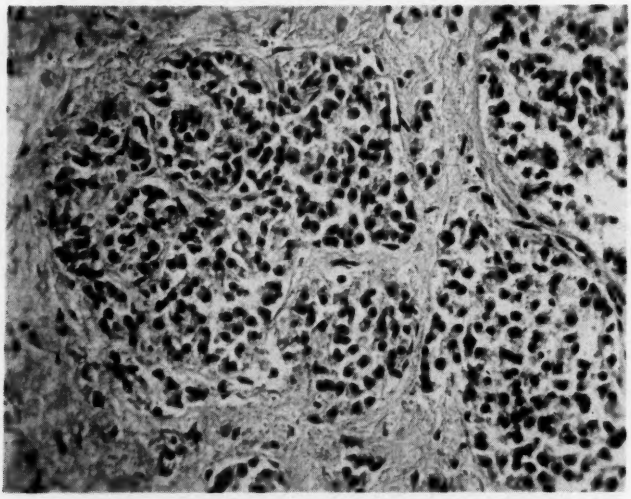


FIG. 5. Carcinoid in lung. Fairly uniform, ovoid cells in acinar nests, imbedded in dense collagen. Hematoxylin and eosin stain; × 300.

nodes, skin, heart, thyroid gland, pancreas, adrenal glands, both kidneys, prostate gland, mesenteric and inguinal lymph nodes, and brain.

DISCUSSION

The tumor had the histologic characteristics of a carcinoid, without argentaffin granules by special stains, and with evidence of anaplasia, as demonstrated by the frequent variation in size and shape of the cells. It was considered to be primary in the lung, first, since it was first demonstrated in this region by x-ray evidence and bronchial biopsy, and second, by the demonstration that the carcinoid tumors present in the duodenum and ileum were polypoid in configuration and were confined to the mucosa and submucosa, failing to invade the muscular coats.

It is not uncommon to find multiple carcinoids in the intestines; in MacDonald's series of 149 extra-appendiceal carcinoids,[3] 16% were proved to have multiple tumors. MacDonald stated that malignant intestinal carcinoids invaded the muscle coats and vascular and lymphatic channels before proceeding to the liver. In his series, widespread metastases were present in 24 cases; all but one involved the liver. In our case, the liver was not involved, further evidence that malignant carcinoid was not present in the intestines.

There is abundant documentation that bronchial carcinoids originate from the surface epithelium or the mucous glands of the bronchus. Liebow[17] believes these tumors arise from mucous glands; in one area of our tumor, tumor nests intermingled with mucous glands, although periodic acid-Schiff stains were negative. In other areas, tumor nests were in close association with the reserve cells of the bronchial mucosa. In some sections there was a resemblance to the reserve or oat cell carcinoma of the bronchus; this similarity was also suggested by the association of Cushing's syndrome with oat cell carcinomas of the bronchus.[12] Nevertheless dissimilarities were apparent, including the carcinoid histologic pattern, the serotonin production, and the slow growth of the tumor. A reserve cell origin of bronchial carcinoids may be considered from the foregoing.

It has been recognized that carcinoids arise only where there are specialized granular epithelial cells of Kulchitsky, or enterochromaffin cells, which have argentaffin properties. Jackson and Konzelman[18] considered the relationship of bronchial adenomas with carcinoids of the gastrointestinal tract and their derivation from neural elements in the bronchi. The close proximity of the lungs and intestine, originating from the foregut in the embryo, provides for a theory of cell misplacement or dormance. Probably the same forces responsible for growth of Kulchitsky cells in the intestine account for similar growth in the lungs. Silver staining granules found in gastrointestinal carcinoids and not demonstrated in bronchial carcinoids are discussed by Warner and Southren.[7] In reviewing the literature, they found only one instance of positive granules in bronchial carcinoids.

A low grade functioning carcinoid in this patient was diagnosed on the basis of minimally but significantly elevated urinary excretion rates of 5-hydroxyindoleacetic acid, the elevated serotonin in the cutaneous nodules, and the rather constant facial flush. Mattingly[4] has stated that it is difficult to give a decisive clinical description or diagnostic criteria of a functioning carcinoid. Without any other known cause of hyperserotonemia, the syndrome would include any case in which there exists a hyperserotonemia, or any abnormal urinary excretion of serotonin metabolite, such as 5-hydroxyindoleacetic acid.

In fact, Southren et al.[19] reported a case of carcinoid syndrome with hyperserotonemia without corresponding 5-hydroxyindoluria. Evidence was presented "that the patient metabolized endogenous serotonin via a different and as yet unknown alternate pathway." Further indication of the variable metabolism in this tumor is a comment by Schneckloth et al.[9] that carcinoid tumor may produce active substances, other than serotonin, which on occasion may account for atypical clinical features. Regarding the insignificant amount of blood serotonin and the lack of classical symptoms, Smith et al.[20] noted that even in patients with significant excess of blood serotonin, symptoms may be very mild and no

simple relationship between blood levels of serotonin and intensity of symptoms can be demonstrated. The results of our studies of serotonin metabolism and urinary function revealed no atypical metabolism of serotonin, and strengthened the belief that this was a malignant carcinoid of low grade function.

The fact that the liver was free from tumor and that no large tumor metastases of appreciable duration existed probably accounted for the mild serotonin effect. It is well known that the metastases of carcinoid tumors in the liver are a rich source of serotonin. Further, it has been suggested that carcinoids in the testis might be a rich source of serotonin. Removal of the carcinoid in the right testicle in the case of Dockerty and Scheifley [21] stopped flushing immediately. In our patient, the enlarged left testis had been removed before any obvious clinical effect of serotonin was noted. The carcinoids in the gastrointestinal tract, being of slow growth, may produce large liver metastases, whereas those in the lung, in addition to the deactivation effect of the amino-oxidase in the lung,[3] produce an overall small quantity of tumor. Hence the intensity of the serontonin effect might be related to the quantity of tumor metastases produced and to the length of time they exist, in addition to the serotonin inhibitor effect.[22]

The infiltration of tumor into the periadventitial tissue of the pulmonary artery, with its consequent narrowing, probably accounted for the pulmonic murmur. This contrasts with the usually ascribed reason for the murmur, namely, diffuse endocardial thickening of the pulmonic valve. This change is ordinarily considered to be the result of the high level of chemically irritating serotonin in the blood of the right side of the heart.

The diffuse metastases in the myocardium, especially in the bases of the right ventricle and interventricular septum, explain the episodes of sinus arrest. Further, the seizures of almost seven years' duration dramatically demonstrate the slow growth of the carcinoid. Sinus arrest has been infrequently reported; those instances due to intrathoracic neoplasms are extremely rare. Davies [23] stated that intrathoracic new growths may cause cardiac arrhythmias in two ways: (1) directly, by invasion of the myocardium or the conducting system, or both; and (2) indirectly, by affecting the vagosympathetic pathways to the heart. The myocardium showed focal fibrosis; this was especially prominent surrounding and coursing through the tumor nodules (Figure 6). Fibrosis in the heart and in other areas, such as in the skin [24] and lungs, may result from the local production of serotonin or inhibitors of serotonin metabolism.[22] Destruction of conducting fibers was evident by the invasion of these fibers in the myocardium by tumor.

Friedberg et al.[25] have stated that prednisone therapy appeared to be effective in abolishing Adams-Stokes syndrome associated with heart block in six patients. This observation is of special interest in our patient since the amelioration of seizures began with the onset of hypercorticism.

The hypercorticism is explained by the hyperplasia of the adrenal cortex, especially of the zona fasciculata. Although much of the adrenal glands was destroyed by the extensive metastases, the hyperplasia of the cortex was probably compensatory. The metastases to the adrenal glands probably occurred late in the course of events, although in sufficient time to allow hyperplasia of the cortex to develop. Several examples of carcinoma (thymus, pancreas, lung) associated with the clinical picture of Cushing's syndrome have been reported.[26, 27]

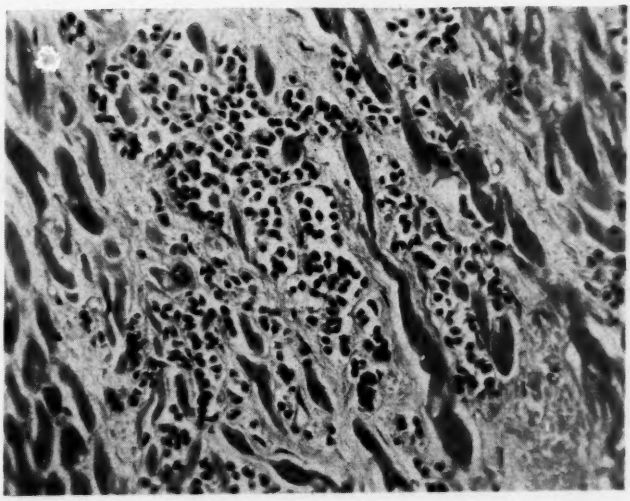


FIG. 6. Metastatic carcinoid in myocardium. Tumor infiltrates the myocardium causing atrophy of muscle, accompanied by fibrous production and replacement. Hematoxylin and eosin stain; × 240.

Kovach and Kyle[12] cited seven cases of Cushing's syndrome associated with bronchogenic carcinoma, all of which were of the oat cell type; the relationship between these two conditions is obscure.

In untreated cases of Cushing's syndrome 50% of the patients survive five years or longer.[12] However, those cases of Cushing's syndrome with malignancy have a rapid downhill course. Thus the short time (approximately four months) between the onset of Cushing's syndrome and death in the presently cited case was characteristic.

SUMMARY

A case is reported of the unique combination of functioning malignant bronchial carcinoid, sinus arrest, and Cushing's syndrome. The functioning aspect of the carcinoid was manifested by flushing, elevated serotonin in the cutaneous metastases, and elevated urinary excretion of 5-hydroxyindoleacetic acid. Sinus arrest was explained by several metastases in the bases of the chambers of the right side of the heart and in the interventricular septum. The adrenal glands which were invaded by tumor masses showed compensatory hyperplasia.

The absence of metastases in the liver and of large tumor masses of appreciable duration probably explains the low grade function of the carcinoid.

The relatively short interval between the onset of Cushing's syndrome and death was characteristic of other cases of Cushing's syndrome associated with malignancy.

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SUMMARIO IN INTERLINGUA

Un mason de racia blanc de 35 annos de etate habeva recurrente episodios de convulsion e inconscientia comenciante in 1952. Roentgenogrammas thoracic monstrava un massa hilar al latere sinistre. Thoracotomia, effectuate in 1955, revelava un massa in le lobo sinistro-superior. Le biopsia de un adjacente nodo e subsequente biopsias de nodulos in le teste sinistre e le pelle esseva comparate, e le diagnose a base de omne le specimens esseva carcinoide maligne con sito primari in le broncho.

Le activitate del carcinoide esseva manifeste in un constante rubor facial, un leve elevation del excretion urinari de acido 5-hydroxyindolacetic, e un augmento del contento de serotonina in un nodulo subcutanee. Tests pro un metabolismo atypic de serotonina esseva negative. Un electrocardiogramma monstrava que recurrente arresto sinusal e asystole esseva le causa del attaccos periodic de septe annos de duration. Tres menses ante su morte, le patiente disveloppava syndrome de Cushing. Un morte rapide post le declaration del syndrome de Cushing in le presentia de un malignitate es characteristic.

Al necropsia extense metastases cardiac esseva trovate, e istos sufficeva a explicar le alterationes electrocardiographic. Le adrenales monstrava extense metastases e hyperplasia. Le absentia de metastases in le hepate explicava probabilemente le basse grado de function del carcinoide.

Isto es le prime reportate caso in que un functionante carcinoide maligne de origine bronchial esseva associate con syndrome de Cushing.

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CARCINOMATOUS NEUROPATHY*

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Introduction

It has long been noted that disorders of the nervous system can occur in association with malignancy and yet be unrelated to the presence of metastases. As far back as 1888 Oppenheim [1] reported the occurrence of peripheral neuritis in malignant disease, and suggested that this was the result of a toxic process. Nonne [2] in 1900 and Siefert [3] in 1902 supported this view. In 1908 Williamson [4] stated that posterior column degeneration had been seen in cases of cachexia

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associated with cancer of various organs, and in 1919 subacute cortical cerebellar degeneration was described in association with neoplasms by Brouwer[5] and Jelgersma.[6] Hassin[7] thought that microscopic metastases explained some of the neurologic findings in malignant disease, but he and Singer[8] stated that chemical or toxic action of the cancer also played a role. In 1922 Lhermitte[9] described a case of chronic cortical cerebellar degeneration and carcinoma of the pancreas. In 1926 Harris[10] discussed polyneuritis associated with carcinoma, and three years later Casper[11] published a report of a case of cortical cerebellar degeneration with recurrent mammary carcinoma. In 1933 Weber and Hill[12] described a patient with polyneuritis and carcinoma of the lung. Subacute cerebellar degeneration accompanying cancer was reported by Parker and Kernohan[13] in the same year, and in 1934 by Greenfield,[14] who suggested a viral etiology. Reports of degenerative lesions occurring at almost any level of the nervous system and associated with visceral carcinoma then became more abundant in the literature.[15–25] In 1948 Wyburn-Mason[26] suggested that a reflex production of peripheral neuritis occurred. In the same year Denny-Brown[27] felt that the primary tumor created a metabolic defect comparable to that seen in vitamin E deficiency. Zülch[28] discussed cortical cerebellar atrophy, and suggested that cases associated with neoplasm were not rare, many dying of the cancer rather than of cerebellar disease. In 1949 Leigh and Meyer[29] noted selective degeneration of the granular layer of the cerebellum in eight cases of visceral carcinoma. Lennox and Prichard[30] in 1950 drew attention to the significant frequency with which peripheral neuropathy accompanied lung cancer. In 1951 Brain et al.[31] reported four cases of subacute cortical cerebellar degeneration, in three of whom there was also degeneration of the long tracts of the spinal cord. In these three cases there was carcinoma, and in two of them the carcinoma was unsuspected during life. In the following year, cases of peripheral neuritis associated with visceral carcinoma without relevant secondary deposits were observed by Elkington[32] and Heathfield.[33] Kremer and Pratt[34] in their case noted a two and one-half-year interval between the onset of the peripheral neuropathy and the first symptoms of the carcinoma. In 1953 Dodgson and Hoffman[35] presented a case of sensory neuropathy with carcinoma of the esophagus, Barroquer-Bordas and Lowenthal[36] reviewed subacute cerebellar degeneration associated with cancer, and Henson[37] published 16 cases of carcinomatous neuropathy, 15 having lung cancer. Also Ironsides[38] had a patient with sensory neuropathy whose bronchial carcinoma could not be found until three and one-half years after the onset of the neurologic symptoms. Henson et al.[39] in 1954 published a clinicopathologic study of 19 patients in whom various neurologic disorders had arisen in conjunction with carcinoma. In 17 of the 19 cases of carcinomatous neuropathy the underlying cancer was situated in the bronchus. In the same year Heathfield and Williams[40] made further contributions, and Greenfield[41] summarized 14 cases. In 1955 Brain and Strauss[42] gave an excellent summary of the subject. In 1956 Charatan and Brierly[43] stressed the mental disturbances in association with carcinoma of the lung in the absence of secondary deposits. Most recently Brain and Henson[44] published their experience with 42 cases of carcinomatous neuromyopathy. In all of these patients there was histologic proof of the diagnosis of carcinoma, while 22 post-mortem examinations insured that the syndromes were not due to metastases.

Case Report

A 59-year-old white married male executive presented himself with the chief complaint of "wobbly legs" for the last two years. He stated that he had been well until two years before, when he had noticed the gradual onset of unsteadiness of gait. This unsteadiness in his lower extremities became progressively worse, and on occasion he would slip and fall. There were no associated pains or paresthesias. Difficulty in walking was worse in the dark, at which time his balance was considerably impaired. With this he noticed a feeling of haziness in his head, some impairment of memory at times, and periods of agitation and depression. He denied vertigo, diplopia, and dysarthria. His family history and past history were noncontributory. He smoked and drank moderately.

On physical examination the patient's weight was 183 pounds, his blood pressure was 190/100 mm. Hg, and his pulse was 88. His skin revealed salmon-colored macules over the trunk compatible with tinea versicolor. Examination of his eyes showed bilateral arcus senilis. There were no vascular changes on visualization of the fundi. The ears, nose, and throat were unremarkable, and there was no generalized glandular enlargement. His neck was within normal limits, and his lungs were clear to percussion and auscultation, with evidence of emphysema. On examination of the heart there was normal sinus rhythm, and no murmurs were present. The abdomen was negative except for diastasis recti. Genitalia were those of a normal male, and the rectal examination was unremarkable. The patient showed a tendency towards a steppage gait, with his legs lifted high, and there was unsteadiness in making quick, turning movements. He had difficulty in attempting to walk a straight line, and fell from one side to the other. He also showed a marked swaying in the Romberg position with his eyes closed, but did fairly well with his eyes open. He had difficulty in balancing on either foot. His muscle tone and muscular strength appeared to be generally quite good, and there was no muscular atrophy. There was a very marked ataxia in the heel-to-knee test bilaterally, but his coordinating tests in the upper extremities appeared to be carried out quite well. There was no disturbance of speech. The tendon reflexes were all present and active, with some decrease in both Achilles reflexes as compared to the others. The abdominal reflexes were decreased on the right as compared to the left. Babinski's sign and Hoffman's sign were absent. However, there was no plantar flexion on stimulation of the feet. Sensation appeared to be normal as to pain, touch, vibration, and joint tendon sense. Cranial nerve functions appeared to be normal. There seemed to be some slight intellectual impairment and memory failure. Laboratory data revealed: hemoglobin of 14.5 gm.%; red blood cell count, 5,213,300/cu. mm.; white blood cell count, 6,750/cu. mm., with 4% bands, 53% mature polymorphonuclear leukocytes, 36% lymphocytes, 6% monocytes and 1% eosinophils; erythrocyte sedimentation rate, 10 mm./hr. A gastric analysis contained 60 ml. of free hydrochloric acid after stimulation with histamine. The urinalysis was unremarkable. Chest x-rays showed evidence of calcium deposits in the right hilum. At the base of the right lung was a circular configuration measuring 6 cm. in diameter, compatible with bullous emphysema. In the left lung there was a patch of increased density, measuring about 1.5 cm. in diameter, behind the left third rib and partly in the third intercostal space. When this chest x-ray was compared with a microfilm taken by the health department one and one-half years previously there was no significant change. A gastrointestinal x-ray series and cholecystogram were unremarkable. A tuberculin (PPD) skin test was markedly positive in the first strength. Sputum examination was negative for tubercle bacilli on smear and culture, and Papanicolaou's stain of the sputum was negative for cancer cells. Vital capacity was 2,400 ml., less than 50% of normal for the patient's surface area. Spirometry revealed that he had a maximal breathing capacity of 62 L., about 60% of normal.

It was decided to place the patient on antituberculous treatment and to follow him very closely. Consequently, he was given 300 mg. of isoniazid and 12 gm. of para-aminosalicylic acid daily. He was seen at monthly intervals during the next nine months. Chest x-rays taken 30 days apart showed no significant change, nor did repeated sputum examinations and sedimentation rates. Nevertheless, there were insidious progression of his ataxia and episodes of dementia. On examination at the tenth month, however, a chest x-ray showed a definite increase in the lesion present at the left apex, in spite of constant antituberculous therapy. This was the first change in the lung lesion to be noted since the first available film had been taken two years previously. It was then decided that patient should have surgery, and a left upper lobectomy was performed. Pathologic examinations of the resected lobe showed a well circumscribed, firm, yellowish-tan mass measuring 4.5 cm. in diameter. This did not communicate with any of the main bronchi. On microscopic examination the mass was found to be a carcinoma, mainly of an anaplastic type, but in some parts of the tumor the cells were suggestive of squamous cell origin. Section of the resected bronchus revealed transition from the relatively normal columnar epithelium to squamous cell metaplastic epithelium. The adjacent lymph nodes were free of any tumor involvement.

The patient has been followed for three years since surgery, and although detailed study has been made, there has been no evidence of metastatic carcinoma in this interval. During the first two years after surgery a slow, progressive increase in his ataxia and dementia occurred. However, a spontaneous remission in the neurologic picture has been manifest for the last year, three years after removal of the lung tumor and five years after the onset of neurologic symptoms.

Discussion

Carcinomatous neuropathy is a loose linkage of various clinical syndromes, in which lesions occur at almost any level of the nervous system in association with neoplasms of the viscera, but unrelated to metastasis. Brain and Henson[44] have broadly classified the group according to their clinical manifestations into those with cortical cerebellar degeneration, those with peripheral neuropathy, those with neuromuscular disorders, and those with mixed forms. The frequency of occurrence of neuropathy in patients with cancer is difficult to assess. Lennox and Prichard,[30] in a retrospective study, found that 1.7% of patients with carcinoma of the bronchus had peripheral neuritis. Henson et al.,[39] also in a retrospective analysis, found an incidence of neuropathy of 11% in patients with bronchial carcinoma. However, one can assume that this is a low estimate, and familiarity with the syndrome in a careful search for cases might well raise this figure. Thus, Henson et al.,[39] because of their awareness of the clinical picture, were able to discover unsuspected carcinoma in 10 patients presenting with neuropathy. As the most common site of the underlying carcinoma is the lung, the increased incidence of lung cancer would also tend to raise this figure. The etiology of the neurologic syndromes is unknown. Carcinotoxins, virus infections, sensitization, and metabolic or endocrine disorders have all been offered as possible explanations, but no firm evidence has been found to support any of them. There is no constant relationship between the course of the neurologic disorder and that of the carcinoma. Neurologic symptoms may antedate the clinical manifestations or diagnosis of the growth by periods of at least three years, or the neuropathy may arise after the successful removal of the cancer. There is also no relationship between the size of the cancer and the

severity of the neuropathy. Thus, severe neuropathy may be present in a patient with a small carcinoma detected only at autopsy, or a patient may show remission from his neurologic disease when dying from the effects of the carcinoma. Treatment has been unrewarding, and even successful surgical removal of the cancer has had no effect on the course of the abnormality in the nervous system.

The case presented here fits classically into the category of cortical cerebellar degeneration. The patient, who was in the later age group, manifested evidence of cerebellar disease of unknown etiology which was progressive over a two-year period. He also presented a pulmonary lesion in the left apex which had been unchanged for at least one and one-half years. When studies failed to indicate a definitive diagnosis, he was followed on antituberculous therapy for a period of 10 months. It was only after the lung lesion suddenly increased in size on x-ray in spite of treatment for tuberculosis that surgery was performed and a bronchogenic carcinoma found. The cerebellar symptoms continued to progress for two years after surgery, when spontaneous remission occurred. When the patient was last seen, three years after removal of the lung tumor and five years after the onset of cerebellar disease, there was no evidence of metastatic carcinoma, and the neurologic symptoms were still in remission.

The importance of the awareness of carcinomatous neuropathy cannot be sufficiently stressed, and early recognition of this disorder presents many points of practical rather than merely theoretic interest. Familiarity with the syndrome may draw attention to the presence of a hitherto undetected neoplasm at a stage when it may still be amenable to treatment. A clue may be obtained when considering the differential diagnosis of a shadow in the lung, and early surgery rather than watchful waiting may be decided upon, to the patient's advantage. A radical surgical approach to a carcinoma with the hope of a cure could well be the decision, rather than a nihilistic attitude due to the erroneous belief that there is metastasis to the nervous system. Finally, in view of the fact that carcinomatous neuropathy is a condition in which there is a marked tendency to spontaneous remission, the prognosis may be one of hope rather than of despair, and may mean a great deal in the management of a case.

Summary

1. Carcinomatous neuropathy is defined as a loose linkage of various clinical syndromes in which lesions occur at almost any level of the nervous system in association with neoplasms of the viscera but unrelated to metastasis.

2. The literature is reviewed.

3. Stress is laid on the importance of recognition of this entity in the diagnosis and management of cases that come to the physician's attention.

4. An illustrative case is reported.

Summario in interlingua

Neuropathia carcinomatose es un designation general coperiente varie syndromes clinic con lesiones a quasi non importa qual nivello del systema nervose, associate con neoplasmas del visceres sed non relationate a metastase. Brain e Henson ha classificate le casos de maniera general secundo lor manifestationes clinic in (1) illos con degeneration cortico-cerebellar, (2) illos con neuropathia peripheric, (3) illos con disordines neuromuscular, e (4) illos a forma mixte. Le frequentia del

occurrentia de neuropathia in patientes con cancere es difficile a evalutar. Henson trovava un incidentia de neuropathia de 11% in patientes con carcinoma bronchial. Le sito le plus commun del subjacente carcinoma es le pulmones. Le etiologia del syndrome neurologic non es cognoscite. Il non existe un relation constante inter le curso del disordine neurologic e illo del carcinoma. Il etiam existe nulle relation inter le dimension del cancere e le severitate del neuropathia. Le tractamento ha essite pauco incoragiante.

Es sublineate le desiderato de prestar attention al possibilitate de neuropathia carcinomatose. Per exemplo, familiaritate con iste syndrome pote resultar in le detection de un neoplasma non previemente notate a un tempore quando illo es possibilemente ancora tractabile. Un umbra in le pulmon pote esser de adjuta in le diagnose differential. Un prompte intervention chirurgic in loco de prolongate observationes es alora ben possibilemente un decision avantagiose ab le puncto de vista del patiente. Un operation radical del carcinoma in le spero de effectuar assi un curation es indicate in tal casos, durante que le erronee conclusion que il se tracta de metastases al systema nervose justificarea un attitude de nihilismo. Finalmente, in vista del facto que neuropathia carcinomatose es un condition con un marcate tendentia a remission spontanee, le prognose pote esser un prognose de spero plus tosto que de despero, un facto que certo vale multo in le tractamento del patiente. Es revistate le pertinente litteratura mundial. Es presentate un caso que illustra le supra-presentate assertiones.

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THE ASSOCIATION OF METASTASIZING BRONCHIAL ADENOMA AND THE FUNCTIONING CARCINOID SYNDROME*

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HEMOPTYSIS, obstructive pneumonitis, and bronchiectasis are well-known complications of bronchial adenomas.[1] It is not generally realized, however, that approximately 10% of bronchial adenomas metastasize to local and to distant sites.[2, 3] During the past 20 years, numerous reports have described local and regional manifestations of metastatic bronchial adenomas. That these tumors are capable of producing the carcinoid syndrome has also become a well established clinical entity. This communication reports another case of the carcinoid syndrome produced by a metastasizing bronchial adenoma.

CASE REPORT

A 50-year-old white female was admitted to Mercy Hospital in August, 1951, complaining of hemoptysis. Three years prior to this admission the patient had experienced a brief respiratory illness characterized by fever, chills, and blood-streaked sputum. Since that time and prior to her admission to the hospital she had experienced occasional episodes of chest pain and hemoptysis. Significant past history included an appendectomy in 1930 and a cholecystectomy in 1935.

Physical examination revealed dullness and diminished breath sounds over the right lower hemithorax. Roentgenogram of the chest disclosed a shadow in the right lower lung field (Figure 1). On September 28, 1951, the patient underwent a right lobectomy. The description of the microscopic pathology was as follows: "This is a bronchial adenoma (adenocarcinoma, grade 1) with ulceration of the overlying mucosa. The cells are fairly uniform and have moderately abundant cytoplasm, with round or oval nuclei. Many have a distinctly eosinophilic cytoplasm. In some areas there is a cylindromatous pattern, but elsewhere the cells lie in sheets separated by small trabeculae of fibrovascular tissue. Mitotic figures are not seen. No metastases were present in the lymph nodes. There were two small local metastases within 2 cm. of the primary site." The immediate postoperative course of the patient was uneventful and she was discharged from the hospital three weeks after surgery.

In November, 1952, approximately 14 months after lobectomy, the patient began

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to experience warm flushing of the chest, neck, and face. During these paroxysms, the skin of the neck and face felt warm and assumed a bluish-red appearance. Each episode was accompanied by abdominal pain, nausea, vomiting, diarrhea, excessive lacrimation, and rhinorrhea. Six specific episodes, each lasting from 12 to 36 hours, occurred between November, 1952, and March, 1953, at which time she was again admitted to Mercy Hospital. Physical examination was within normal limits except for well healed thoracotomy and abdominal scars, and a questionable right upper quadrant abdominal mass. There was no hypertension, cardiomegaly, murmurs, or abnormal pulmonary sounds. Laboratory studies, including tests of liver function, were unremarkable. Chest roentgenograms showed the post-lobectomy changes, including partial resection of the right seventh rib and slight elevation of the right hemidiaphragm. Radiographic studies of the gastrointestinal tract, including small

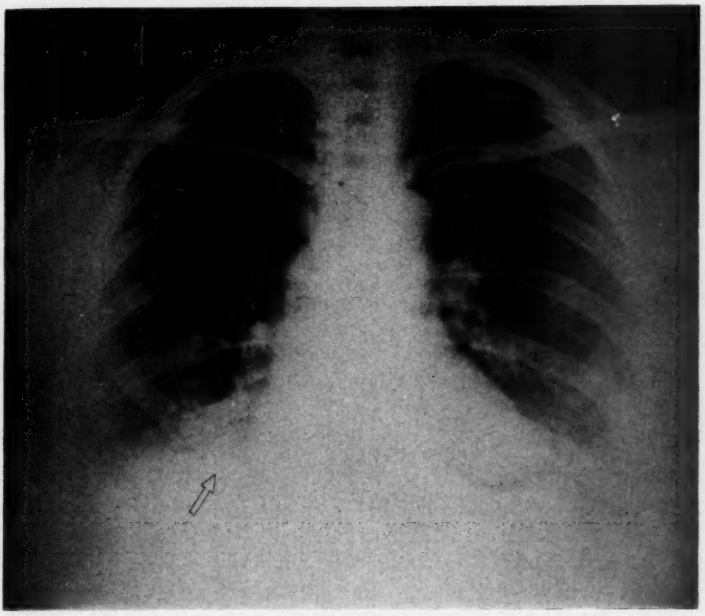


FIG. 1. Roentgenogram of the chest showing primary lesion in the right lower lung field.

bowel studies, were normal. Her physician attributed her symptoms to the menopause, which she had actually experienced uneventfully two years previously. A multitude of medications including antihistamines, epinephrine, androgens, estrogens, barbiturates, and intravenous glucose were given without any apparent benefit.

In May, 1954, because of a severe episode of nausea, vomiting, and abdominal cramps, she was admitted to another hospital where an exploratory laparotomy was performed. The only abnormal finding was extensive involvement of the liver with metastatic tumor. No primary gastrointestinal site could be found. Biopsy (Figure 2) revealed "metastatic tumor of liver from primary malignant adenoma of lower lobe of right lung."

With increasing frequency, approximately once a week, the patient continued to

experience episodes of facial flushing, dizziness, nausea, vomiting, and diarrhea. Because of severe right upper quadrant abdominal pain and marked hepatomegaly, her physician recommended Co^{60} radiotherapy to the liver area. From October 3, 1955, to December 8, 1956, she received 2300 r over the liver, with some relief of symptoms. For the first time, the patient was placed on oral chlorpromazine, and she reported definite symptomatic relief of her paroxysmal attacks of flushing and gastrointestinal disturbances.

Follow-up study in July, 1956, and again in January, 1957, revealed a moderately firm, nodular liver extending 12 cm. below the right costal margin. Because of increasing abdominal discomfort, she received two separate courses of radiotherapy to the central liver area during the next 18 months.

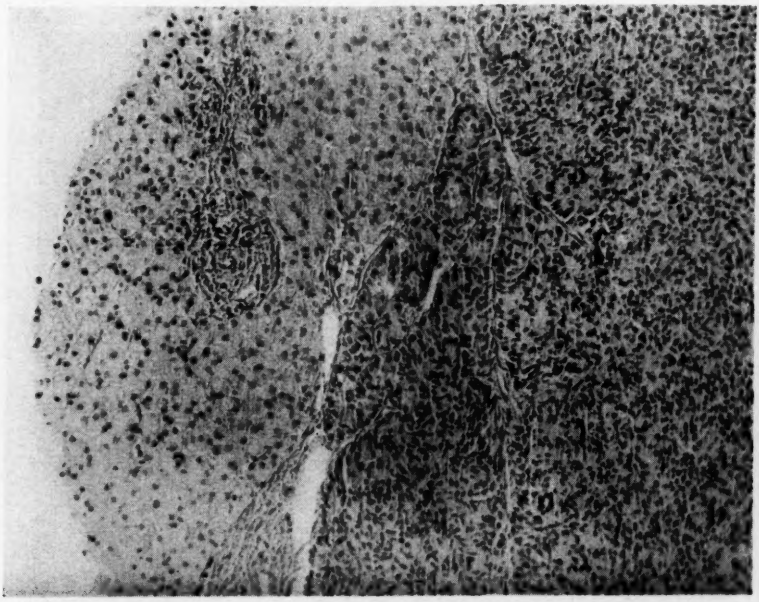


FIG. 2. Section of liver biopsy showing carcinoid tumor adjacent to normal liver tissue. Hematoxylin and eosin stain, original magnification × 100.

The patient was readmitted to Mercy Hospital on May 19, 1959, because of severe abdominal pain, nausea, and vomiting. Episodic flushing, accompanied by respiratory wheezing, and explosive diarrhea were now becoming more pronounced. Physical examination on this admission revealed a well developed but moderately dehydrated thin female. The pulse was regular at 100 per min. and the blood pressure was 98/70 mm. Hg. The skin over the patient's upper chest, neck, and face was warm and appeared to be a deep, fiery red. Conjunctival suffusion with increased lacrimation was also noted. There was no significant adenopathy. Examination of the thorax revealed generalized hyperresonance with diffuse rhonchi and expiratory wheezes. There was no cardiomegaly, but a rough grade 2 systolic murmur was heard in the third intercostal space just to the left of the sternum. The liver was moderately firm and nodular, and again extended 12 cm. below the right costal margin. There was minimal pretibial edema.

Laboratory studies disclosed a mild hypochromic, microcytic anemia, but normal values were reported for urinalysis, blood serologic tests, blood sugar, and blood urea nitrogen. A bromsulfalein test showed 10% retention in 45 min. and the alkaline phosphatase was 17.3 Bodansky units. Liver scan, following the intravenous injection of 420 μc. of Robengatope, revealed that "much of the liver has probably been replaced by tumor." Strongly positive qualitative tests for 5-hydroxyindoleacetic acid (5-HIAA) were obtained on several occasions and a 24-hour collection of urine revealed 157 mg. of 5-HIAA (normal, 2 to 9 mg).

A gastrointestinal series, including a very careful study of the small bowel, was entirely normal. A roentgenogram of the abdomen disclosed an enlarged liver containing calcific densities (Figure 3). An electrocardiogram was interpreted as being within normal limits.

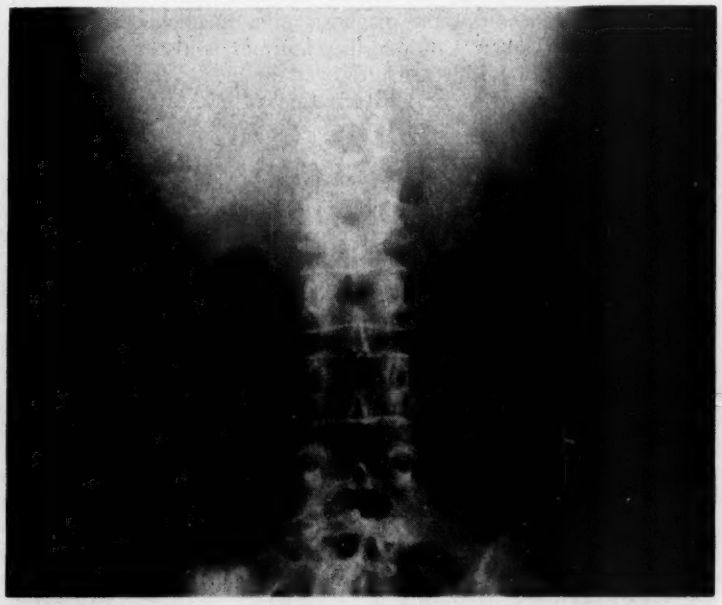


FIG. 3. Roentgenogram of the abdomen showing marked enlargement of liver shadow and amorphous calcifications.

During the patient's hospitalization of approximately three weeks, she experienced five severe episodes of flushing, respiratory wheezing, and diarrhea lasting from three to 24 hours. These symptoms appeared to be effectively ameliorated by the oral administration of chlorpromazine. At this writing, the patient is still living and has shown no significant change.

DISCUSSION

In this patient, the marked histologic similarity of the bronchial adenoma to that seen in the hepatic metastases 32 months later furnishes convincing evidence that they are the same tumor. Consideration of other primary sites would seem unlikely. An appendectomy in 1930 and a cholecystectomy in

1935 failed to show any evidence of carcinoid tumor in the resected organs. Abdominal exploration in May, 1954, showed metastatic involvement of the liver without revealing a primary gastrointestinal site or any evidence of mesenteric nodal metastases. Bowel wall invasion and spread to regional lymph nodes, characteristic features of malignant intestinal carcinoids, were not noted at laparotomy. Since then, several radiographic examinations of the entire gastroinestinal tract, including careful small bowel studies, have all been negative. Rectal and ovarian sites have also been excluded by appropriate examinations. The bulk of evidence, therefore, is against the possibility of another primary site.

The seven-year history of intermittent flushing, associated with diarrhea and respiratory wheezing, and the finding of a markedly increased urinary excretion of 5-HIAA, confirm the diagnosis of a functioning carcinoid syndrome. The later development of a cardiac murmur is also noteworthy. The subsequent appearance of calcific densities over the liver area is of considerable interest. Whether these represent calcification of necrotic tumor tissue or heteroplastic bone formation as described by Hulley and others cannot be stated with certainty at this time.[4, 5]

McBurney and others noted a large number of liver metastases in their review of metastasizing bronchial adenomas.[2] No mention, however, was made of a symptom complex suggestive of the carcinoid syndrome. That such a relationship might exist was first suggested by Mattingly.[6] A case of bronchial adenoma and liver metastases complicated by severe diarrhea was reported by Kincaid-Smith and Brossy in 1956.[7] However, urinary levels of 5-HIAA were not obtained.

To the best of our knowledge, our patient represents the eighth reported case of a functioning carcinoid syndrome produced by a metastasizing bronchial adenoma.[8–11] In six of these cases, including our patient, there was histologic confirmation of liver metastases. Each of these patients had elevated levels of urinary 5-HIAA and manifested the well-known features of the functioning carcinoid syndrome, with episodic cyanotic flushes and diarrhea predominating. The other two patients had increased serotonin content in the bronchial adenoma but showed no definite evidence of liver metastases.[9] Neither of these patients experienced facial flushing or diarrhea, and the determination of urinary 5-HIAA was normal in the one patient in which it was performed. This experience with bronchial adenomas has been similar to that found with gastrointestinal carcinoids.[12–14] In the latter, most patients have not developed symptoms or elevated levels of 5-HIAA until the tumor has metastasized to the liver.

Like gastrointestinal carcinoids, these tumors have shown a slow growth rate. In most of these patients there was a considerable lapse of time, ranging from three months to six years, between the pulmonary surgery and the onset of the carcinoid syndrome. Although medical management has not proved to be very satisfactory, many patients survive long symptomatic periods. The patient presented in this report is still living approximately seven years after the development of the carcinoid syndrome. She, as well as others, obtained symptomatic relief from chlorpromazine. When feasible, adequate resection of hepatic metastases has proved to be beneficial. In one patient with a metasta-

sizing bronchial adenoma, the urinary levels of 5-HIAA returned to normal after removal of a solitary metastatic liver mass.[10]

Although the histogenesis of bronchial carcinoids is not definitely known, a few workers have suggested that these tumors may be related to argentaffinoma of the gastrointestinal tract. In spite of this morphologic resemblance, most investigators have been unable to demonstrate the typical argentophile staining characteristics in bronchial adenomas or in hepatic metastases.[1, 15, 16] Unfortunately, this staining technic was not applied to the tissue in our case. Nevertheless, in view of the case presented herein and the other cases described in the literature of the functioning carcinoid syndrome produced by metastasizing bronchial adenoma, there would appear to be more than just a coincidental relationship between bronchial carcinoids and carcinoids originating in extrapulmonary sites.

Summary

Another case of a functioning carcinoid syndrome produced by metastasizing bronchial adenoma has been reported. The authors believe that this is the eighth recorded case. A brief review of this syndrome has been presented, and differences from and similarities to gastrointestinal carcinoids are described briefly.

Addendum

After completing this paper, the patient in this report died, approximately seven and one-half years after the onset of the carcinoid syndrome. Unfortunately, the patient died at another hospital and there was no post-mortem examination.

Since this manuscript was prepared for publication, Williams and Azzopardi have reported two cases of the carcinoid syndrome associated with bronchial tumors (Williams, E. D., Azzopardi, J. G.: Tumours of the lung and the carcinoid syndrome. Thorax **15**: 30, 1960). Their first case was a follow-up account of the patient originally reported by Kincaid-Smith and Brossy.[7] The second case was an oat-cell carcinoma with widespread metastases.

Acknowledgment

The authors wish to express their appreciation to Dr. Deha Gersey Owen, of the University of Pittsburgh Graduate School of Public Health, who performed the quantitative urinary 5-HIAA studies.

Summario in Interlingua

Approximativemente 10% de omne adenomas bronchial resulta in metastases in sitos local o distante. Recentemente il ha essite demonstrate que iste tumores es etiam capace de producer le functionante syndrome carcinoide. Le autores crede que le patiente presentate in iste reporto representa le octave reportate caso del syndrome carcinoide producite per un metastasante adenoma bronchial.

Le 28 de septembre 1951, post un historia de tres annos de febre intermittente, de dolores thoracic, e de hemoptysis, un feminina de racia blanc de 50 annos de etate esseva subjicite a lobectomia dextero-inferior. Le resecate specimen revelava un adenoma bronchial con duo micre metastases local. Dece-quatro menses plus tarde le patiente comenciava experientiar intermittente episodios de rubor ignicolor del facie, accompaniate de dolores abdominal, nausea, vomito, diarrhea, excessos de lacrimation, e rhinorrhea. In maio 1954, post un episodio sever de nausea, vomito, e dolor abdominal, le patiente esseva subjicite a chirurgia abdominal. Le laparotomia revelava un extense affection del hepate con tumor metastatic. Le biopsia hepatic revelava "metastatic tumor hepatic ab maligne adenoma primari del lobo pulmonar dextero-inferior."

Le sequente cinque annos in le curso del patiente esseva characterisate per repetite

episodios de rubor facial, nausea, vomito, e diarrhea. In maio 1959, fortemente positive tests esseva obtenite pro acido 5-hydroxyindolacetic (A5-HIA): un collection de 24 horas de urina revelava 157 mg de A5-HIA.

A causa de dolores abdominal in le quadrante dextero-superior e de marcate hepatomegalia, le patiente recipeva tres separate cursos de radiotherapia applicate al area hepatic central, con un certe alleviamento del symptomas. Un melioration additional esseva effectuate per chlorpromazina oral.

Le similitude histologic del adenoma bronchial con le metastases hepatic es un forte prova que il se tractava del mesme tumor in le duo sitos. Exploration abdominal e repetite examines radiographic del vias gastrointestinal total ha revelate nulle signo de un altere sito primari.

Viste le numerose similitudes il pare justificate supponer un relation plus que simplemente coincidental inter carcinoides bronchial e carcinoides a origine in sitos extrapulmonar. Como il es characteristic de carcinoides gastrointestinal, iste tumores ha monstrate un lente crescentia, e le majoritate del patientes non ha disveloppate symptomas o elevate nivellos de A5-HIA usque post que le tumor se habeva metastasate ad le hepate. Ben que le majoritate del travaliatores non ha succedite a demonstrar le presentia de typic granulos argentaffin in carcinoides bronchial o in depositos metastatic, il remane un facto que le similitude con carcinoides a origine in le vias gastrointestinal es marcate ab le puncto de vista morphologic.

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RENAL TUBULAR HYPERCHLOREMIC ACIDOSIS WITH BONE DISEASE: A CASE REPORT*

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RENAL acidosis resulting from tubular insufficiency without glomerular insufficiency is a relatively uncommon entity.[1-14] It is accompanied frequently by calcification and stone formation in the kidney and occasionally by osteomalacia. The relative roles of hypercalciuria, systemic acidosis, and parathyroid activity in the pathogenesis of these complications are not certain, although Albright and colleagues postulated that parathyroid hyperplasia develops secondary to the renal loss of calcium. The primary disturbance, however, is clearly a failure of the kidney to excrete acid in a normal manner.

The excretion of acid and the conservation of base is one of the major functions of the kidney. This is normally accomplished by two mechanisms: (1) the production of ammonion ion by the renal tubular cells to exchange with fixed cations in the tubular urine, and (2) the acidification in the tubules of filtered buffers, mainly phosphate, to produce an acid urine. If the kidney tubules are damaged, a decrease in the ability to excrete acid urine and to produce ammonium exists, and the body must find some other source of readily available cation to take the place of the latter. Calcium, potassium, and sodium are the most available cations and will be excreted in increased amounts in the urine. Calcium appears to be one of the most readily available, and clinically significant hypocalcemia occurs in this situation as a result of the hypercalciuria. According to Albright's hypothesis, parathyroid hyperplasia occurs under the stimulus of the hypocalcemia. The excess parathyroid hormone will result in an attempt to raise the blood calcium level by increased resorption of bone, and because of its primary action, will lead to increased excretion of phosphorus in the urine. The absence of disturbed glomerular function permits the hyperphosphaturia to occur. This attempt to raise the blood calcium and to maintain it in a normal range may, however, be unsuccessful because of the continuous excretion of calcium in the urine, and the serum calcium level will remain in the low or low-normal range. The low or low-normal serium calcium, plus the low serum phosphorus, which has resulted directly from parathyroid-induced hyperphosphaturia, will result in the failure of deposition of calcium salts in newly formed osteoid tissue. Bone which is not properly calcified is increasingly susceptible to strain. This leads to increased osteoblastic activity, which in turn produces an increase in serum alkaline phosphatase.[3]

Renal losses of potassium and sodium are also important. A low potassium syndrome with paralysis and characteristic electrocardiographic changes has been reported as a result of renal acidosis.[1, 11, 15] Hypernatriuria with resultant hyponatremia may result as well, and symptoms suggestive of low salt syndrome may develop. With the continued loss of cations, acidosis results, and the carbon dioxide combining power falls. This is coupled with chloride retention, which apparently occurs because of the inability of the kidney to conserve bicarbonate.

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The exact etiology of the tubular disturbance is unknown. Whether it represents a primary tubular defect or a tubular defect secondary to some inflammatory or metabolic disturbance is not evident. Urine cultures were generally negative, and in only one case was healed pyelonephritis found at autopsy.[1] Post-mortem examination of another case showed extensive vacuolation of the tubules and an alteration in the type of epithelium.[5] There was no evidence of chronic vascular disease or glomerulonephritis. There has been some controversy as to whether the renal calculi and nephrocalcinosis which accompany this form of renal acidosis are the causes or the results of the disturbances in renal function. Albright and Reifenstein, in reviewing the known cases up to 1948, found that two had had neither the renal calculi nor nephrocalcinosis.[1] This, plus the fact that with proper therapy these patients stop forming stones, strongly favors the idea that the renal calcification is the result rather than the cause of the renal lesion.

Osteomalacia of this type must be differentiated from the other conditions listed above. In renal rickets, otherwise called renal osteitis fibrosa generalisata, there is evidence both of glomerular and tubular damage of long duration. The urea nitrogen is elevated as a result of the glomerular lesion, and acidosis is associated with retention of the blood sulfates and phosphates, and the inability of the tubules to produce ammonia and to excrete a sufficient amount of acid. Hypocalcemia develops, followed by parathyroid hyperplasia. X-rays show generalized decalcification of the bones which results from the acidosis and is similar to that seen in osteitis fibrosa generalisata due to primary hyperparathyroidism. The elevated blood urea nitrogen and phosphorus, plus a normal blood chloride, differentiate this syndrome from the others under consideration.

Fanconi's syndrome presents renal glycosuria, hypercalciuria, hyperphosphaturia, and increased amino acids in the urine. There are decreased serum phosphorus and bicarbonate, increased alkaline phosphatase, and normal or low serum calcium. Here, again, renal tubular acidosis is present and again is associated frequently with rachitic and osteomalacic bone disease.

Simple hypercalciuria, for lack of a better term, results in renal lithiasis. There is no basic disturbance in acid-base balance or in the kidneys' ability to form ammonia or excrete an acid urine. The same sequence of events noted above may lead to secondary hyperplasia of the parathyroids if the hypercalciuria is severe and uncompensated for by increased intake or absorption of calcium.

Case Report

A 52-year-old white female was seen by her local physician with the complaint of pain in the knees and lower extremities and was treated symptomatically. Three months later she returned complaining of weakness and a weight loss of 15 pounds. She was referred to me for an opinion at this time. The medical history was nonrevealing except for the complaints noted above.

Physical examination showed a well developed, thin white female whose blood pressure was 100/64 mm. Hg. The pulse was 78 per minute. There was a large mass deep in the right upper quadrant of the abdomen which was thought to be renal in origin. The remainder of the examination was normal.

Laboratory studies were as follows: hemoglobin, 11.6 gm.%; leukocytes, 9,300/cu. mm.; differential, normal; urine pH, 6; specific gravity, 1.006 to 1.008; albumin, 1-plus; pyuria, present. Urine culture was negative. The average blood calcium

was 9.2 mg.%, with variations from 8.7 to 9.3 mg.%; phosphorus, 2.5 mg.% (normal, 3 to 4.5 mg.%); alkaline phosphatase, 25 King-Armstrong units; carbon dioxide combining power, 17 mM./L.; chloride, 113 mEq./L.; blood urea nitrogen, 13.5 mg.%; sodium, 141 mEq./L.; potassium, 4.2 mEq./L. Phenolsulfonphthalein excretion was only 18% in two hours. A urinary concentration test produced a maximal specific gravity of only 1.012, while a dilution test produced a minimal specific gravity of 1.001. In order that the calcium excretion in the urine could be followed, the patient was placed on a low calcium, neutral ash diet (130 mg. of calcium per day). At the end of five days on this diet, 597 mg. of calcium were excreted in the urine in 24 hours. Normal urinary excretion of calcium on this diet should not be over 100 mg. of calcium per day. Urinary ammonia excretion was 0.45 gm./L. (normal, 0.6 to 1.0 gm./L.). X-rays of the long bones showed early osteomalacia. Chest

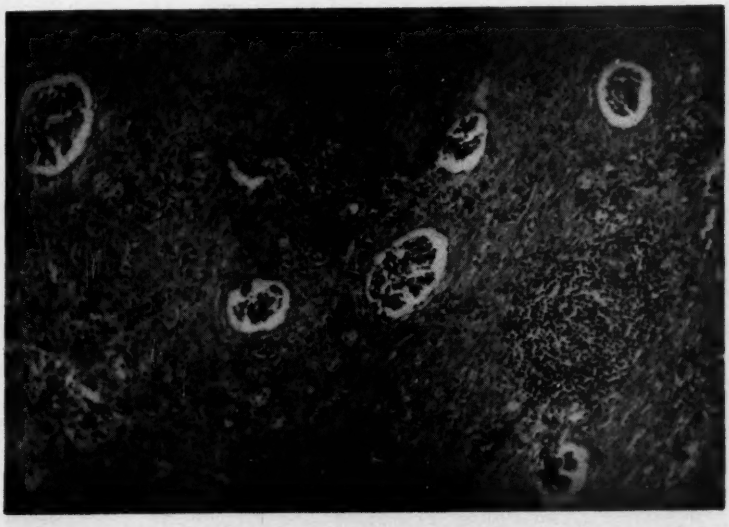


FIG. 1. Low power magnification of a section of renal parenchyma to show normal glomeruli and extensive tubular atrophy.

x-ray was negative. An intravenous pyelogram showed multiple bilateral renal calculi.

A diagnosis was made of renal acidosis, with osteomalacia secondary to tubular insufficiency without glomerular insufficiency and with secondary hyperparathyroidism.

The patient was placed on 100 ml./day of a mixture of 98 gm. of sodium citrate and 140 gm. of citric acid dissolved in 1 L. of water in an attempt to control the acidosis. She was also given 15 gm. of calcium gluconate and 50,000 units of vitamin D daily to combat the osteomalacia, and was referred back to her local physician.

One month later the patient's physician performed a right nephrectomy because of intractable pain secondary to a large staghorn calculus in the right renal pelvis. The patient had taken the sodium citrate–citric acid mixture only occasionally because it nauseated her. She had, however, taken the calcium and vitamin D daily.

Laboratory studies at the time of surgery were as follows: calcium, 9.8 mg.%; phosphorus, 3.2 mg.%; alkaline phosphatase, 18.5 King-Armstrong units; carbon dioxide combining power, 15 mM./L.; chloride, 100 mEq./L.

Grossly the kidney was enlarged (12.5 by 9 by 8 cm.) and fluctuant. One hundred milliliters of viscid gray liquid were present in the renal pelvis; this liquid was cultured and was sterile. A large staghorn calculus was tightly wedged in the renal pelvis. The stone weighed 32 gm. The kidney without the stone weighed 225 gm. The calyces were dilated, and smaller stones were present in several of the calyces. The renal cortex was from 6 to 8 mm. thick.

Microscopic sections of the kidney showed "very extensive tubular atrophy, more marked in the cortex than in the medulla. The remaining cortical tubules are small and some of them have very low epithelium and almost approach capillaries in appearance. These small tubules are separated by very dense fibrous tissue with a light patchy lymphocytic infiltrate. Most of the cortex is 2 or 3 mm. thick. The glomeruli appear relatively normal, although a very few hyaline glomeruli are seen. The blood vessels are not remarkable. The medulla shows considerably less fibrosis with a patchy infiltration of lymphocytes and plasma cells. The pelvic mucosa is

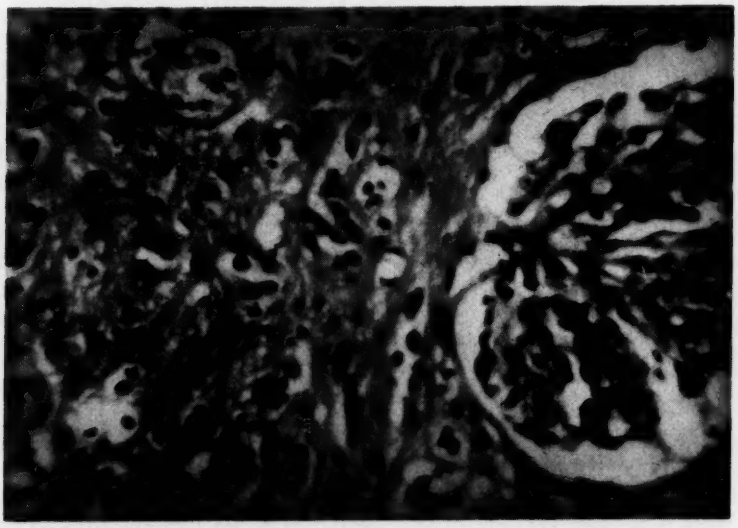


FIG. 2. High power magnification of an area of Figure 1.

very heavily infiltrated by lymphocytes and plasma cells, and in some areas it is ulcerated with granulation tissue, macrophages, and neutrophilic leukocytes. There is a very occasional calcified focus in a tubule, but these are about 1 cm. apart and are microscopic in size."

The patient was reinstructed in the use of the sodium citrate–citric acid mixture and started on it again. The calcium and vitamin D were continued.

The patient was next seen by me one month after surgery. She had been taking the prescribed medication properly. Laboratory studies showed: carbon dioxide combining power, 20 mM./L.; chloride, 111 mEq./L.; calcium, 9.8 mg.%; phosphorus, 3.2 mg.%.

The patient was not seen again for two years. Her complaints when seen then were of aching and gnawing pain in the arms and legs and generalized weakness. She had again stopped taking the sodium citrate–citric acid mixture of her own accord. She had been taking the calcium and vitamin D intermittently.

Physical examination revealed tenderness on pressure over the bones of the arms and legs. The blood pressure was 104/82 mm. Hg. The examination was otherwise normal.

Laboratory studies showed the following: hemoglobin, 15.4 gm.%; leukocytes, 10,300/cu. mm.; differential, normal; urine: specific gravity, 1.010; pH, 7; albumin, 1-plus; 20 to 25 white blood cells per high power field. The calcium was 9.5 mg.%; phosphorus, 2.8 mg.%; carbon dioxide combining power, 15.8 mM./L.; chlorides, 131 mEq./L.; alkaline phosphatase, 26.5 King-Armstrong units; sodium, 149 mEq./L.; potassium, 3.9 mEq./L. blood urea nitrogen, 16 mg.%. Phenolsulfonphthalein excretion was 14% in the first 15 minutes and 65% in two hours.

The patient was again placed on a neutral ash, low calcium (130 mg. calcium per day) diet for four days. At the end of this time she excreted 327 mg. of calcium per day in the urine.

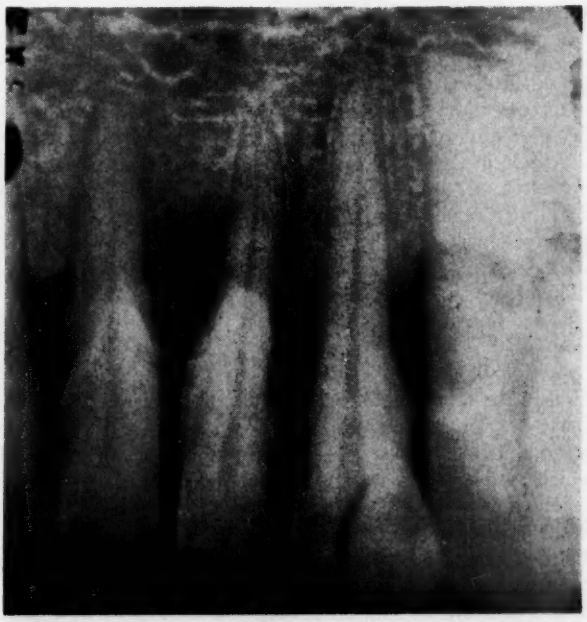


FIG. 3. Dental film, showing resorption of the lamina dura.

X-ray of the kidneys, ureter, and bladder showed innumerable small calcified shadows, varying in size, overlying the left kidney. There was generalized osteoporosis of the long bones which was noted by the roentgenologist to be consistent with hyperparathyroidism. Dental films showed resorption of the lamina dura about the teeth.

The patient had, in essence, returned almost to the state she had been in two years previously because she had not continued the necessary treatment.

DISCUSSION

To recapitulate, a relatively rare renal lesion is described in which tubular damage predominates, producing tubular insufficiency insofar as the production

of ammonia and an acid urine is concerned. The case reported fulfills the criteria necessary for the diagnosis:

1. Tubular insufficiency is indicated by the inability to concentrate urine, the markedly diminished phenolsulfonphthalein excretion, and the decreased quantity of ammonia in the urine.
2. The relative lack of glomerular insufficiency is attested to by the normal blood urea nitrogen and normal urine dilution test.
3. Microscopic sections show widespread tubular atrophy and relatively normal glomeruli.
4. Acidosis is evidenced by a low carbon dioxide combining power.
5. The low-normal calcium, low phosphorus, high alkaline phosphatase, hyperchloremia, and hypercalciuria while the patient was on a low calcium diet serve to complete the picture.

This is not to say that the glomeruli are not affected. There may well be widespread renal disease, as indicated by hyalinization of a very few glomeruli in the microscopic sections cut from the kidney in this case. However, there is not sufficient glomerular impairment to produce a disturbance of function. Further, the vessels in the renal parenchyma appeared to be normal microscopically. The decreased ammonia formation by the tubules necessitates the excretion of another readily available cation. The cation, calcium, fulfills this need, and hypercalciuria with hypocalcemia results. This may lead to parathyroid hyperplasia which, in turn, produces hyperphosphaturia and hypophosphatemia. This, in turn, results in a defect of calcification of osteoid tissue and elevation of the alkaline phosphatase level.

The etiology of the syndrome is unknown. There is no evidence that pyelonephritis is an etiologic factor. In the case reported here, cultures of the urine and of the fluid in the renal pelvis were sterile. There was no evidence of renal vascular disease or glomerulonephritis.

There is good evidence, as noted earlier in this paper, that the nephrocalcinosis which is present is not the primary lesion, but is secondary to the tubular metabolic defect.

This case in particular points up the need for twofold treatment in this condition. Treatment must be aimed at (1) correction of the acidosis, and (2) provision of calcium to return the osteomalacic bone to normal. Albright et al.[3] have described a mixture of sodium citrate and citric acid in water which will effectively restore the acid-base balance to normal, since the organic radicle is burned in the body and the cation is available for urinary excretion. This, unfortunately, will do very little to restore the depleted calcium to normal, since even if all the calcium absorbed by the gastrointestinal tract were retained, it would be years before a positive calcium balance could be achieved, inasmuch as the amount of calcium lost in the urine during the active phase of the disease has been excessive in quantity. Therefore, calcium and vitamin D are given to correct this aspect of the problem.

The patient described here was placed on medication as mentioned above, but soon stopped taking the sodium citrate-citric acid mixture because of anorexia, although she continued to take the calcium and vitamin D. When she was studied again, the calcium and phosphorus levels had returned to normal

and the alkaline phosphatase had decreased, but the acidosis remained severe. When this situation was discovered the medications were started again in proper amounts, and in one month the acid-base balance was restored to normal. Later the patient again stopped taking the sodium citrate-citric acid mixture, and used the calcium and vitamin D only intermittently. The acidosis returned, excessive quantities of calcium were excreted in the urine, hyperchloremia and hypophosphatemia occurred, and it was evident from the x-ray films that the associated bone disease was still present.

Summary

A case is described of osteomalacia and nephrolithiasis secondary to renal tubular acidosis. One kidney was removed with a staghorn calculus, and the pathologic structure was examined; the damage was primarily in the tubules.

The patient exhibited the chemical findings of acidosis without azotemia, low-normal calcium levels, and hypophosphatemia. These signs of chemical osteomalacia were further supported by x-ray evidence of osteomalacia. The patient was treated with a solution of sodium citric acid and with supplementary calcium and vitamin D.

The differential diagnosis and treatment are discussed, as well as the factors involved in the production of osteomalacia, including secondary hyperparathyroidism.

Acknowledgment

The author is indebted to Dr. Ralph Olson for referring this case to him.

Summario in interlingua

Es describite un caso de osteomalacia e nephrolithiasis secundari a acidosis reno-tubular. Un ren esseva excidite con un calculo coralliforme. Le structura pathologic esseva examinate. Le lesion afficeva primarimente le tubulos.

Le patiente exhibiva le constatationes chimic de acidosis sin azotemia, de nivellos infero-normal de calcium, e de hypophosphatemia. Iste signos de osteomalacia chimic esseva supportate additionalmente per indicios roentgenologic de osteomalacia. Le patiente esseva tractate con un solution de citrato de natrium e supplementos de calcium e de vitamina D.

Le diagnose differential e le tractamento es discutite, como etiam le factores participante in le production de osteomalacia, incluse hyperparathyroidismo secundari.

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SYMPTOMATIC OSTEOMALACIA SECONDARY TO CLINICALLY OCCULT CAUSES *

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The purpose of this report is to describe two adult patients with disabling osteomalacia. The feature worthy of emphasis in each case is the negligible symptomatology referable to the organ systems believed to be the sites of the primary defects—in the first case, the gastrointestinal tract with occult steatorrhea; in the second, the kidneys with latent tubular acidosis.

Case Reports

Case 1. A 50-year-old housewife was first seen by us in February, 1959, complaining of stiffness and generalized aching pain in her back and both lower extremities. The pain was not well localized. The onset of symptoms was insidious, and had been slowly progressive for about 11 months. Any movement, particularly walking, was performed with great difficulty because of increased pain and stiffness. A cane was used for support. Episodes of stiff fingers had been noted infrequently for 10 years. A 10-pound weight loss without anorexia was associated with this illness. There was no family history of a similar affliction.

Past history revealed an episode of watery diarrhea in 1947 which had lasted for several months. No blood or steatorrhea had been noted. The concentration

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of hemoglobin was 10.5 gm. per 100 ml., with an erythrocyte count of 3,870,000 per cubic millimeter. A phenolsulfonphthalein test revealed that 23% of the dye was excreted in 15 minutes. Other pertinent laboratory data are found in Table 1. X-rays, including an upper and lower gastrointestinal series, were normal. The diarrhea subsided with symptomatic therapy, but its cause was not determined. Also significant in the past history were two episodes of massive hematuria (December, 1957, and August, 1958). A complete examination, including cystoscopy and retrograde pyelography, failed to reveal any pathology. At this admission there were no complaints referable to the gastrointestinal or urinary tracts. The patient's dietary history was perfectly adequate except that she did not drink milk. Other dairy products, however, were frequently consumed. She craved citrus fruits.

TABLE 1

Pertinent Data on Case 1

		Date									
		1947		1959							
		8/11	8/15	2/15	2/16	2/17	2/18	2/19	2/20	3/19	4/19
Urine	Reaction—pH	Acid	Acid	Alk.		6.5		5.8	5.5	6.4	6.1
	Specific gravity	1.012	1.001	1.001							
	Calcium (mg./day)			18	10	12	15	20	12	5	35
Serum	NPN (mg./100 ml.)	66	53								
	BUN (mg./100 ml.)			13							
	Calcium (mg./100 ml.)	7.2	9.2	6.9	6.8	7.6				8.5	7.4
	Phosphorus (mg./100 ml.)			3.9	3.8	4.3					
	Alkaline phosphatase										
	K.A. (1–10 U./100 ml.)					27					
	B.L. (0.8–2.3 U./100 ml.)									4.6	6.7
	CO_2-combining power (mEq./L.)					23			19.8	22.5	
	Chloride (mEq./L.)					105			117	105	
Acid load with NH_4Cl (gm./day)							←4→				
Rx	Calcium gluconate (gm./day)								←3→		
	Vitamin D_2 (units/day)								←100,000→		

Physical examination revealed a tall, thin woman weighing 105 pounds. She had a peculiar, high-step, waddling gait, as if her back and thighs were extremely stiff and painful when moved. Her blood pressure was 100/70 mm. Hg. Excellent dental hygiene was noted. No suggestion of a vitamin deficiency was found. Examination of the heart, lungs, and abdomen revealed normal findings. A pelvic examination was not remarkable. The stool was grossly normal. Motion was not limited except by pain. No tenderness to palpation was elicited. The neuromuscular examination was within normal limits except for the Achilles tendon reflexes, which were not obtained. No signs of latent tetany were elicited.

X-rays revealed slight demineralization of the skeleton and symmetric "pseudofractures" in both femoral necks (Figure 1). In retrospect, loops of distended small bowel were apparent in this roentgenogram. No other Milkman's fractures were demonstrated, even after a complete bone survey. A barium meal, barium

enema, and intravenous pyelogram were considered normal. It is noteworthy that when films taken in September, 1958, were reviewed, the "pseudofractures" were also found.

Laboratory Data: Hemoglobin, 11 gm. per 100 ml.; red cell count, 3,160,000 per cubic millimeter; white cell count, 4,200 per cubic millimeter, with a normal differential; corrected sedimentation rate, 35 mm. in one hour. The erythrocytes were slightly macrocytic. Urinalysis and blood sugar were normal. The serum protein, cholesterol, sodium, and potassium concentrations were normal. Urine amino acid nitrogen and tubular phosphorus reabsorption studies were normal. However, the serum concentration of carotene was diminished (65 μg./100 ml.), and the prothrombin time was prolonged (14.5 sec., with a control of 11 sec.). A 72-hour stool specimen averaged 25.4 gm. total fat per day, and this constituted 54% of the dry

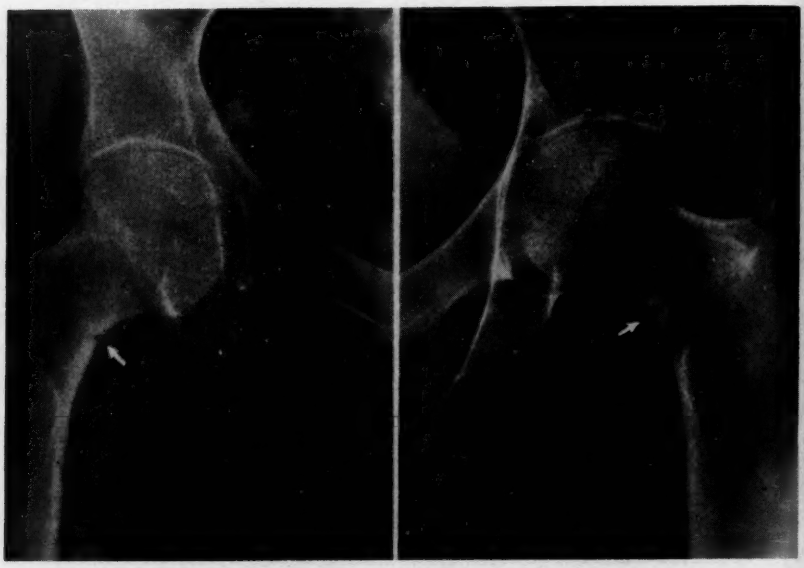


FIG. 1. *Case 1.* X-ray of the pelvis, demonstrating the symmetric location of "pseudofractures." Note also the distended loops of small bowel.

weight. Other pertinent data are found in Table 1. The quantitative urinary calcium determinations were made while the patient was on a regular diet.

The patient was then released on an alkaline ash diet low in fat, multivitamins, 3 gm. of calcium gluconate daily, and 100,000 units of vitamin D_2 daily. One month later she was markedly improved. No pain or stiffness was noted. She was able to walk several blocks without difficulty, and her gait seemed much more natural.

Case 2. A 53-year-old housewife was referred to this hospital in March, 1957, with a tentative diagnosis of multiple sclerosis. Her chief complaints were pain, stiffness, and weakness in her back and legs, so severe that she was unable to walk. This illness had begun insidiously in the spring of 1954, when pain was first noted in her right lower extremity. She was forced to drag her right leg and to use a cane when walking. Soon the pain and stiffness spread to her back and both lower extremities, causing her to walk with a waddling gait. The pain was generalized,

constant, aching, and aggravated by movement of any kind. These symptoms progressed so far that she was placed in a nursing home in 1956, and she had been bedfast for several months prior to this admission. No parasthesias, visual disturbances, or uncoördinated movements were noted. Moderate anorexia and a 20-pound weight loss were associated with this illness. There was no family history of a like affliction.

Past history revealed an episode of hematuria, dysuria, and frequency of urination in 1933. An examination at that time, including cystoscopy, revealed a kidney infection, which responded promptly to treatment. The patient remembered several bouts of "bladder infection" that were less severe following this. At this admission, nocturia was the only urinary tract complaint. Her food intake was probably not adequate in the 1940s because of irregular eating habits, a dislike for milk, and a liberal alcoholic intake. After 1950, however, her diet seemed well balanced. Her



FIG. 2. *Case 2.* X-ray of the pelvis in 1957, demonstrating the symmetrical location of "pseudofractures."

left leg had been fractured three times (1949, 1950, and 1952), each following a minor fall.

Physical examination revealed a chronically ill, thin woman weighing 105 pounds. She was unable to stand or walk because of marked pain aggravated by movement. The blood pressure was 120/80 mm. Hg. Her skin was diffusely tanned, and increased facial hair was noted. She was edentulous. No abnormalities of the heart, lungs, or abdomen were found. A pelvic examination was not remarkable. The stool was grossly normal. Rather marked dorsal kyphoscoliosis and tenderness to palpation over the spine were noted, and even passive movements of the legs seemed to aggravate the pain. However, the entire neuromuscular examination was otherwise within normal limits.

X-rays revealed bilaterally symmetric "pseudofractures" involving the femoral necks, pubic rami, fibulae, scapuli, and ribs (Figure 2). There was suggestive evidence of another pseudofracture in the left tibia. Spine films confirmed the

TABLE 2

Pertinent Data on Case 2

		Date																			
		1957							1958			1959									
		3/7	4/1	4/4	4/9	4/15	4/23	11/19	5/1	9/15	10/15	2/25	2/26	3/1	3/2	3/3	3/4	3/5	3/6	3/7	3/12
Urine	Reaction—pH	Alk.	Acid		Alk.	Alk.	Acid					Acid	Acid	Acid	6.7	6.3			5.4	5.6	
	Specific gravity	1.006	1.008		1.004	1.004	1.003					1.009	1.007	1.005							
	Calcium (mg./day)					90	24								48		75	100	130	140	20
Serum	NPN (mg./100 ml.)		41	43	55	55	53	25													
	BUN (mg./100 ml.)		24						19			18			16						18
	Calcium (mg./100 ml.)	9.4	8.9			9.9	9.2			10.9		8.8			10.0		10.8			9.3	
	Phosphorus (mg./100 ml.)	2.7	2.0			3.0	2.7				3.1	2.7			2.8		3.2			3.4	
	Alkaline phosphatase																				
	K.A. (1–10 units/100 ml.)	16.2	13.2			12.2	10.4			20.4	15										
	B.L. (0.8–2.3 units/100 ml.)											3.1					3.1				
	Albumin/globulin ratio (gm./100 ml.)					3.6/2.0	3.3/1.8	5.0/1.3				4.2/1.3									
	CO_2-combining power (mEq./L.)		17.7	17	20	18	16			21		24			27		23			14	26
	Chloride (mEq./L.)			111		122	113			101		109			103		106			116	108
	Potassium (mEq./L.)			5.6		5.6	5.9			5.2		4.6			5.0		5.1			4.9	4.9
	Sodium (mEq./L.)			137		140	142					134			140		140			140	135
Acid load with NH_4Cl (gm./day)																	←—— 4 ——→				
Rx	Dicalcium phosphate (gm./day)						←—— 3 ——→														
	Calcium lactate (gm./day)								←—1—→											←— 2.5 —→	
	Vitamin D_2 (units/day)						←—2,000—→		←—50,000—→											←—50,000—→	
	Shohl's mixture (ml./day)																			←— 30 —→	

marked kyphoscoliosis of the thoracic vertebrae, but showed no evidence of demineralization. Pyelography demonstrated bilateral hydronephrosis and a right hydroureter. Ptosis and slight rotation of the right kidney were also noted.

Laboratory Data: Hemoglobin, 13 gm. per 100 ml.; red cell count, 4,400,000 per cubic millimeter; white cell count and differential, normal. Multiple urinalyses were normal; however, one specimen revealed a faint trace of albumin. In a phenolsulfonphthalein test, 3% of the dye was excreted in 15 minutes. The urea clearance was 47% of normal. Blood sugar and liver function studies were normal. Sulkowitch's test was consistently negative. Other pertinent laboratory data appear in Table 2. The quantitative urine calciums were determined while the patient was on a 150-mg. calcium diet.

While the patient was hospitalized, a urinary tract infection was treated with antibiotics. She was then placed on 3 gm. of dicalcium phosphate and 2,000 units

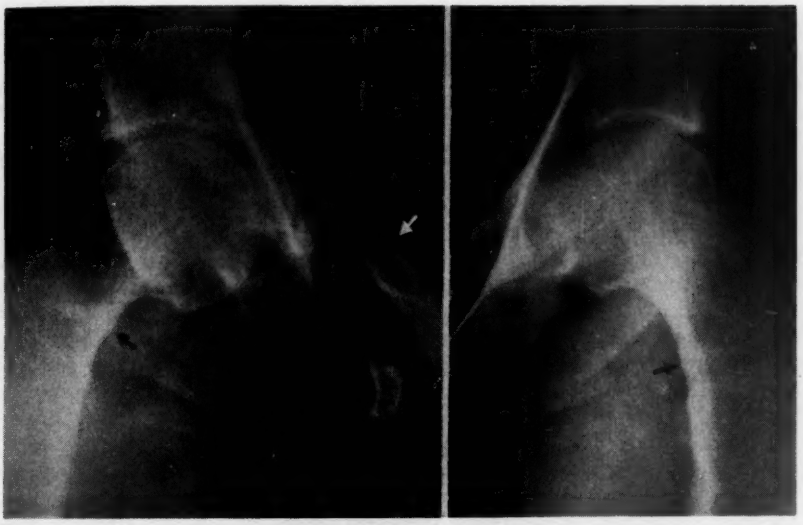


FIG. 3. *Case 2.* X-ray of the pelvis in 1959, showing partial remineralization of the "pseudofractures."

of Vitamin D_2 daily. Physical therapy contributed diathermy, muscle exercises, and gait training. She could soon walk short distances with the aid of a cane, but she remained quite stiff, and moved with a peculiar waddling and shuffling gait. After discharge she was followed irregularly in clinic. One year later (April, 1958) she continued to complain of back and lower extremity pain, and she still found walking quite difficult. Her medication was changed to 1 gm. of calcium lactate and 50,000 units of vitamin D_2 daily. Within two months she was able to move about much better, and there was no longer any pain or stiffness. This dramatic improvement continued through February, 1959, even though she had stopped all medication for more than three months. She was readmitted at this time for further diagnostic studies. The physical examination was not changed from the previous admission except for the marked improvement in all movements, especially walking. No stiffness, pain, or weakness was demonstrated.

X-rays of the skeletal system showed definite improvement, with partial recalci-

fication of the "pseudofractures" (Figure 3). The intravenous pyelograms remained unchanged.

Laboratory studies revealed a hemoglobin of 14.3 gm. per 100 ml. Several urinalyses were normal. A phenolsulfonphthalein test showed 15% excretion of the dye in 15 minutes. A urea clearance was 32% of normal. A urine culture was negative. Liver function studies were normal. A 72-hour stool specimen averaged 2.3 gm. total fat per day. A serum creatinine was 1.4 mg. per 100 ml. The urine amino acid nitrogen was 463 mg. per 24 hours (within the normal range), and the tubular reabsorption of phosphorus was 88% (within normal limits). Other pertinent data are found in Table 2.

Quantitative urine calcium determinations were made while the patient was on a regular diet. She was given a three-day acid load with ammonium chloride (4 gm./day), and the urine pH and calcium were determined along with the serum carbon dioxide capacity and chloride (Table 2).

The patient was then released on an alkaline ash diet, 2.5 gm. of calcium lactate daily, 50,000 units of vitamin D_2 daily, and 30 ml. of Shohl's mixture (140 gm. citric acid and 98 gm. sodium citrate dissolved in 1 L. of water) daily.

Comment

It seems clear that most of the symptoms in each case may be attributed to osteomalacia. The complaints of generalized aching pain in the back and lower extremities, a peculiar waddling gait, stiffness, and weakness despite an otherwise relatively normal neuromuscular examination were well described by Milkman.[1] The resultant disability certainly seemed strikingly out of proportion to the abnormalities demonstrated by physical examination in our patients. Yet it was the discovery of "pseudofractures" that first called attention to the proper diagnosis, and the laboratory data later established both cases as typical of moderately severe osteomalacia. Since both clinical manifestations and abnormalities in serum calcium, phosphorus, and alkaline phosphatase determinations may appear long before radiographic signs, [1, 2] it seems reasonable to believe that this disorder in our patients was of long standing.

The assignment of a pathogenetic mechanism for the production of the severe osteomalacia in these patients was initially quite perplexing, and remains questionable in the second case. It seems proper to consider that clinically occult steatorrhea is the underlying cause in the first patient. She denied diarrhea or copious, fatty, foul-smelling, light-colored stools with this illness. However, laboratory studies indicating a macrocytic anemia, decreased absorption of carotene and vitamin K, and an increased fat content in the stool quite satisfactorily established the diagnosis of a malabsorption syndrome. The history of hematuria suggested renal calculi and a possible calcium-losing renal tubular defect; however, urine calcium studies were quite low, and the patient secreted an acid urine. Although in response to an acid load her serum chloride rose slightly higher than normal, the carbon dioxide capacity did not fall excessively, and so this was not considered a significant abnormality. We have assumed, therefore, that the osteomalacia resulted from inadequate absorption of vitamin D and minerals.

It is well recognized that the steatorrhea associated with malabsorption syndromes is not always persistent, but may be characterized by remissions and exacerbations. Furthermore, it may occur without clinically evident diarrhea

or stool abnormalities.[3] Juergens et al.[4] recently reported five cases emphasizing that malabsorption syndromes may present with classic symptoms of osteomalacia (a secondary manifestation), yet with few complaints or none referable to the gastrointestinal tract (the site of the primary defect). Our first patient is a case in point, and again stresses the necessity of considering occult steatorrhea as a hidden cause of osteomalacia.

Explaining the mechanism which provoked osteomalacia in the second case is somewhat more perplexing. Steatorrhea seems adequately excluded. Although the patient offered no complaints suggestive of kidney pathology, there is unquestionable evidence of anatomically and physiologically significant renal disease, as judged by intermittent bouts of urinary tract infection, x-ray evidence of bilateral hydronephrosis, decreased urea clearance, a diminished ability to excrete phenolsulfonphthalein, and an apparent lack of means for concentrating the urine. That it is primarily a "tubular rather than glomerular insufficiency" [1] is supported by the symptomatic osteomalacia, the relatively slight azotemia, the low serum phosphorus, and the frequently alkaline urines associated with a persistent hyperchloremic metabolic acidosis in 1957.

The cardinal feature of renal tubular acidosis, as it is usually described, is an inability to secrete an acid urine, with a resultant hyperchloremic acidosis and excessive urinary loss of calcium and potassium.[5] Nephrocalcinosis, nephrolithiasis, osteomalacia, profound muscle weakness, and polyuria with decreased ability to concentrate the urine are often described as complications of the excessive cation loss. Because these features may present in a variety of combinations, there is considerable variation in the clinical patterns. Certainly there is variation in the severity of this renal defect, since totally asymptomatic cases have been reported in family studies.[6, 7] All patients, then, with renal tubular acidosis do not demonstrate signs of calcium wasting. However, in most cases associated with osteomalacia, evidence of hypercalciuria is found. This is to be expected, since it is the excessive urinary wastage of calcium that is presumed to be the causal factor. It is disturbing, therefore, that we were unable to demonstrate renal stones, nephrocalcinosis, or hypercalciuria in the second case. Urinary calcium excretion was normal (60 mg./24 hrs.) during control studies with case 5 of Albright's series.[8] He attributed this to a slightly alkaline ash diet employed during the study, and well demonstrated that urine calcium is markedly increased by an acid ash diet. Urine calcium increased threefold in our patient while she was taking ammonium chloride. Albright et al.[8] further suggested that, when osteomalacia is long-standing and the skeleton is well depleted of minerals, the urinary calcium wastage will decrease somewhat. These, plus the possibility of variation in the severity of the renal tubular defect (see below), are possible explanations for our failure to find hypercalciuria.

Amino-aciduria and glucosuria were not demonstrated in this case. The tubular reabsorption of phosphorus was well within accepted limits, and the serum content was not unusually low. Furthermore, our patient has shown clinical, chemical, and radiographic improvement with the usual doses of vitamin D. For these reasons it is felt that the rarer causes of osteomalacia, such as Fanconi's syndrome with multiple tubular defects [9, 10] or vitamin D-resistant rickets,[11] are not applicable in this case.

While a more precise definition of the etiology responsible for producing

osteomalacia in the second patient would require additional studies, we feel that in 1957 the evidence pointed to renal tubular acidosis. It is interesting, then, that studies in 1959 did not demonstrate an overt hyperchloremic acidosis, even though therapy had been stopped for three months. However, a latent defect in tubular acidification was easily shown by administering an acid load. This was judged by an excessive fall of the carbon dioxide capacity (14 mEq./L.) and an excessive rise in serum chloride (116 mEq./L.). That this is an abnormal response is supported by the studies of Reynolds.[12] While taking ammonium chloride, our patient's urine pH dropped to 5.4. Do these findings suggest that the tubular defect has improved, or that it intermittently changes in severity? It is well known that children with renal tubular acidosis often recover spontaneously. In adults, however, even though treatment with alkalizing agents may correct clinical symptomatology, the underlying tubular defect is usually not modified. The idea that tubular defects may vary in magnitude from time to time in a given case is poorly documented; however, it seems reasonable, and is tentatively postulated as an explanation for the lack of an obvious hyperchloremic acidosis in 1959. Elkinton et al.[13] reported a case of renal tubular acidosis with improvement similar to ours—that is, the metabolic acidosis changed from an overt manifestation to a latent defect, found only by adminstering an acid load. Until a better understanding of the precise factors producing renal tubular acidosis is achieved, we cannot be sure whether changes in the tubular defect toward normal are apparent or real. Nevertheless, this patient certainly demonstrates the importance of considering an asymptomatic and latent tubular defect as an obscure cause of osteomalacia.

Summary

Two patients with disabling osteomalacia are presented because they emphasize that this state may arise from mechanisms that are obscure. Occult steatorrhea was found in the first patient, although complaints referable to the gastrointestinal tract were negligible. Evidence to support renal tubular acidosis is presented in the second case, although symptoms suggesting renal disease and signs of hypercalciuria were minimal. It is postulated that the tubular defect was improved two years later, having changed from an overt manifestation to a latent defect.

Summario in Interlingua

Es reportate le casos de duo femininas adulte con invalidante symptomas de osteomalacia, comportante le typic constatationes chimic e "pseudofracturas." Un aspecto que merita esser sublineate in le un e le altere caso es le negligibile symptomatologia attribuibile al systemas organic reguardate como le sitos del defectos primari. In un del duo subjectos, le presentia de un occulte steatorrhea esseva fiinalmente demonstrate per indicios laboratorial de malabsorption, incluse anemia macrocytic, reducite absorption de carotena e vitamina K, e augmento del contento de grassia in le feces. Le secunde patiente habeva pauc symptomas urinari, sed in illa indicios radiographic esseva presente de hydronephrosis bilateral. Esseva etiam constatate un reducite clearance de urea, un reducite excretion de phenolsulfonphthaleina, e un plus marcate dilution del urina. Que iste disordine renal resultava in un acidosis tubular esseva evidente in 1957, viste le presentia de sever osteomalacia, acidosis hyperchloremic con urinas relativemente alcalin, basse concentrationes del

phosphoro seral, e un solmente leve azotemia. Il es additionalmente de interesse que in 1959 le acidosis tubular esseva multo minus evidente, e il esseva solmente post cargation acide con chloruro de ammonium que un significative reduction del capacitate del sero de combinar CO_2 esseva producite. Es postulate que in iste patiente un variation in le severitate del defecto tubular esseva presente. Ambe iste patientes se meliorava con le regime usual de 50.000 unitates de vitamina D e sales de calcium.

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EDITORIALS

RENAL TUBULAR ACIDOSIS

THE physician sees many patients with acidosis due to renal failure. The great majority of these are patients with either acute tubular necrosis or chronic contractive disease of the kidney. In such patients glomerular function and tubular function are diminished in parallel and the patient becomes not only acidotic but azotemic, and hence this common type of acidosis has been called *uremic acidosis.* There is another and less common type of renal acidosis that has come to be labeled *renal tubular acidosis.* In this syndrome the tubular function is impaired to a greater extent than is glomerular function. The difficulty is not due primarily to a decrease in total number of functioning "intact" nephrons but rather to specific and sometimes genetically determined abnormalities in one or more of the tubular mechanisms for the excretion of acid. This type of renal acidosis, the subject of a number of papers in this issue, is mainly characterized by systemic hyperchloremic acidosis with little or no azotemia and a weakly acid, neutral, or alkaline urine.

If renal tubular acidosis is so rare, why is it important for the physician to be cognizant of its pathophysiologic and diagnostic features? The answer is that it is treatable. This is in contrast to uremic acidosis seen in the late stages of chronic glomerulonephritis where treatment is severely limited by the inexorable character of the disease and at best is merely palliative. In renal tubular acidosis, on the other hand, simple oral therapy with alkali will usually arrest the progress of the physiologic disturbances and, more importantly, the serious and sometimes fatal complications that commonly ensue. These protean complications are deposition of calcium in the kidney and urinary tract with secondary pyelonephritis, decalcification of the skeleton, muscle weakness and paralysis due to potassium loss, and all the ill-starred sequelae of sodium depletion and dehydration. In the arrest of such complications treatment is literally life-saving. For this reason alone the physician should turn his attention to this relatively rare disturbance. And in addition, study of this clinical disturbance gives entrance to a fascinating path of exploration in the fields of physiology, biochemistry, and genetics.

The first step in this exploration is to consider the clinical circumstances in which this type of renal acidosis has been found. In 1936 Butler, Wilson, and Farber [1] first described such an acidosis in infants with a type of renal calcification that had been reported by Lightwood [2] in the same year. The first adult case of this type of acidosis was reported as such in 1945 by Baines

[1] Butler, A. M., Wilson, J. L., Farber, S.: Dehydration and acidosis with calcification at renal tubules. J. Pediat. **8**: 489, 1936.
[2] Lightwood, R.: Communication No. 1. Arch. Dis. Child. **10**: 205, 1935.

Barclay, and Cooke.[3] In 1946 Albright, Burnett, Parson, Reifenstein, and Roos [4] published their famous monograph in which they recognized that certain cases of osteomalacia were due to renal tubular acidosis or, as they labeled it more exactly but less briefly, *tubular insufficiency without glomerular insufficiency*. Since then, renal tubular acidosis has turned up in infants and in adults, in many clinical circumstances that may be classified roughly into six groups, as follows.

The first group is that of infantile renal tubular acidosis which appears during the first year of life, occasionally with nephrocalcinosis, and usually with a defect in tubular reabsorption of water; this type is mainly characterized by recovery by the end of 24 months of life (if alkali therapy has been adequate). The second group is that of late primary renal tubular acidosis in adults and older children. In this group it usually is associated with nephrolithiasis and nephrocalcinosis, frequently is found with osteomalacia or rickets, and sometimes is familial. The third group consists of those children and adults who exhibit renal tubular acidosis as part of the Fanconi syndrome. This syndrome is characterized by multiple tubular defects leading to aminoaciduria, glycosuria, and hyperphosphaturia. It may be familial and in younger patients usually is associated with cystinosis. The fourth group has recently been described by Lowe and colleagues [5] and has been labeled the cerebro-oculorenal syndrome. The chief characteristics in this group of infants and small children are the occurrence of mental retardation and cataracts or other eye lesions along with the renal tubular acidosis. The latter, in this syndrome, is thought to be due to a specific defect in the renal tubular production of ammonia, but the physiologic and biochemical characteristics of this group remain to be clearly defined. The fifth group is that in which renal tubular acidosis occasionally has been found in association with other inborn errors of metabolism including galactosemia, nephrogenic diabetes insipidus, and Wilson's disease. And finally, there are certain patients with chronic pyelonephritis in whom tubular damage and tubular acidosis appear to occur out of proportion to the variable degree of nephron destruction. Quite obviously the multiple clinical settings and varied associations of this specific dysfunction of the renal tubule indicate its pathogenetic and etiologic complexities.

An adequate understanding of the pathogenesis of this disturbance has been made possible in recent years by the investigations of such physiologists as Pitts, Berliner, Gilman, Schwartz, Relman, and others. These workers have clarified the three main processes by which the normal kidney excretes acid. The first of these is the reabsorption of bicarbonate by a process of

[3] Baines, G. H., Barclay, J. A., Cooke, W. T.: Nephrocalcinosis associated with hyperchloraemia and low plasma-bicarbonate. Quart. J. Med. **14**: 113, 1945.

[4] Albright, F., Burnett, C. H., Parson, W., Reifenstein, E. C., Jr., Roos, A.: Osteomalacia and late rickets. The various etiologies met in the United States with emphasis on that resulting from a specific form of renal acidosis, the therapeutic indications for each etiological sub-group, and the relationship between osteomalacia and Milkman's syndrome. Medicine **25**: 399, 1946.

ion exchange, hydrogen for sodium; here the active process is the sodium pump. If the accompanying sodium of all filtered bicarbonate is exchanged, the resultant carbonic acid breaks down to carbon dioxide and water and no bicarbonate is excreted. The second process is the acidification of filtered buffers, mainly phosphate. Here the active process is the hydrogen pump which moves hydrogen ion against a high concentration gradient, i.e., makes a urine quite acid relative to the extracellular fluid. The total quantity of acid or hydrogen ion so excreted is measurable as the titratable acidity of the urine. The third process is the conversion of ammonia that has been produced in the tubular cell to ammonium ion (containing a fourth hydrogen); this ion is then exchanged for a filtered sodium. The total net amount of hydrogen ion or acid excreted in the urine per unit time, therefore, may be measured as the sum of the excretion rates of titratable acid plus ammonium minus bicarbonate.

In renal tubular acidosis the first two of these processes are impaired: hydrogen ion is not exchanged either passively or actively for sodium ion to a normal degree. The result is that an abnormal amount of bicarbonate is excreted in an insufficiently acid urine containing relatively little titratable acid; ammonium excretion appears to be inhibited only secondarily by the relative alkalinity of the tubular urine.[6, 7] In all three processes hydrogen ion is made available in the tubular cell by action of the enzyme, carbonic anhydrase, but investigators of this disorder have been unable to implicate a defect in this enzyme either indirectly by studies of the effect of the enzyme inhibitor, acetazoleamide,[8–11] or directly by renal biopsy.[12] Defective enzymatic reactions in the Krebs tricarboxylic cycle have also been suspected since these are probably the source of energy for the active tubular transport of sodium and hydrogen ion; experimental administration of maleic acid, an inhibitor in vitro of enzymes containing sulfhydryl groups (including succinic dehydrogenase), has been shown to interfere with the tubular transport of glucose, phosphate, amino acids, and hydrogen ion.[13] But in

[5] Lowe, C. U., Terrey, M., MacLachlan, E. A.: Organic aciduria, decreased renal ammonia production, hydrophthalmos, and mental retardation. A clinical entity. Amer. J. Dis. Child. **83**: 164, 1952.

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[12] Yaffe, S. J., Craig, J. M., Fellers, F. X.: Studies on renal enzymes in a patient with renal tubular acidosis. Amer. J. Med. **29**: 168, 1960.

[13] Berliner, R. W., Kennedy, T. J., Hilton, J. G.: Effect of maleic acid on renal function. Proc. Soc. Exp. Biol. Med. **75**: 791, 1950.

the only study to date of biopsy material no defect was demonstrated in carbonic anhydrase, glutaminase, or TPN diaphorase.[12] The biochemical pathogenesis of renal tubular acidosis has still to be clarified.

The etiology of renal tubular acidosis likewise continues to be uncertain. Originally, Albright and his colleagues postulated that the tubular defect was acquired as the result of ascending infection in the kidney; Lathem [14] has reported four patients in whom the stigmata of renal tubular acidosis appeared to be the result of pyelonephritis. But this type of acidosis is rare and pyelonephritis is common. The defect sometimes appears to be a secondary manifestation of certain inborn errors of metabolism (see above) and of several endocrinopathies such as hyperthyroidism [15] and primary hyperparathyroidism.[16] Certainly the book is not yet closed on acquired etiologic factors.

In an effort to examine the other causes of primary renal tubular defects in acid excretion, the editors have recently reported elsewhere [17] an analysis of 162 cases in the literature of the syndrome in which the renal tubular acidosis was uncomplicated by other tubular defects or other primary diseases. It was immediately apparent that these cases comprised at least two disease entities that could be differentiated on the basis of age of onset, sex distribution, incidence of recovery, and family involvement. Eighty-seven of the patients had an onset during the first year of life, two-thirds of them were male, a majority completely recovered, and they showed very little familial involvement; these cases may be labeled infantile primary renal tubular acidosis. The other 75 cases (including five of our own) either began between the first and tenth year, or after puberty, were two-thirds female, did not appear to recover, and showed a considerable degree of familial involvement; these must have a different disease which may be called late primary renal tubular acidosis. In the infantile form certainly a developmental defect is to be suspected because of the spontaneous recovery. McCance and Hatemi [18] have clearly demonstrated the progressive development over the first year of life of the infant's ability to excrete acid; if a defect in such development is involved, its cause is not apparent. If there is a genetic factor in the infantile syndrome, it must be a recessive trait since only three siblings and no parents were affected.

A genetic etiology, however, is clearly involved in many of the late primary cases. Of the 21 cases with information concerning their families, in eight there were manifestations of the disease in other siblings and in six of

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[15] Huth, E. J., Mayock, R. L., Kerr, R. M.: Hyperthyroidism associated with renal tubular acidosis. Amer. J. Med. **26**: 818, 1959.

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[18] McCance, R. A., Hatemi, N.: Control of acid-base stability in the newly born. Lancet **1**: 293, 1961.

these more than one generation was involved. One of these families with by far the most extensive involvement (four generations) is reported in detail by Randall in this issue. All these data point to the etiologic role of a dominant autosomal gene with considerable variation in penetrance and expressivity.

The evident variation in expressivity or clinical manifestations of this defect raises the possibility that latent or subclinical cases are present in the population. The question is brought up by the case report of Powell and Deiss in this issue and has been examined by the editors in the family of one of their cases.[17] Using the refined criterion of a hydrogen ion "clearance" index, we found that some of the clinically well children of our proposita showed a defect in excreting acid when challenged with an acid load (a standard dose of ammonium chloride). Such a test is analogous to the detection by physiologic challenge of heterozygotes of phenylketonuria and of galactosemia, and should be useful in extending our knowledge of the genetics of this disease. The chief hurdle to acquiring this knowledge, however, is the lack of information about relatives of patients. Here is a great opportunity for a real contribution in the field of genetics by practicing physicians, as suggested by one of us in these columns recently.[19]

There are other perplexing problems to be found in the syndrome of late primary renal tubular acidosis; one of these concerns the metabolism of calcium and phosphorus. In our review we found that 45% of the patients in the late group exhibited osteomalacia or rickets and 77% nephrocalcinosis, nephrolithiasis, or both. The chances are that a majority of patients will present themselves to the physician because of the complication of renal stones. As Johnson has pointed out in his paper in this issue, hypercalciuria was thought by Albright and his colleagues to lead to a secondary hyperparathyroidism, as reflected by the hypophosphatemia that is seen so commonly in this condition. But no sure evidence for this chain of events has ever been adduced, nor has the direct effect of acidosis on bone ever been assessed adequately. The role of the urinary excretion of citrate in this disease remains an enigma. It has been reported that citrate excretion is low in these patients and does not return to normal levels during alkali therapy,[20, 21] that it is not related to concomitant potassium depletion.[22] Dedmon and Wrong found low rates of citrate excretion in their patients when it was related to the urinary pH (although intracellular pH in renal tubular cells has been thought to be the main determinant[23]).

[19] Huth, E. J.: Editorial. Propositi, physicians, and papers. Ann. Intern. Med. **54**: 583, 1961.

[20] Bauld, W. S., MacDonald, S. A., Hill, M. C.: Effect of renal tubular acidosis on calcium excretion. Brit. J. Urol. **30**: 285, 1958.

[21] Dedmon, R. E., Wrong, O.: Excretion of citrate in patients with renal tubular acidosis and nephrocalcinosis. J. Lab. Clin. Med. **56**: 802, 1960.

[22] Morrissey, J. F., Ochoa, M., Lotspeich, W. C., Waterhouse, C.: Factors influencing citrate excretion in renal tubular acidosis. Clin. Res. **9**: 206, 1961.

[23] Crawford, M. A., Milne, M. D., Scribner, B. H.: The effects of changes in acid base balance on urinary citrate in the rat. J. Physiol. **149**: 413, 1959.

It is not yet clear to what extent urinary citrate excretion is depressed due to excessively low tubular cell pH and to reduction in total mass of functioning renal tissue. For these reasons it is not known whether citrate is a primary or a secondary factor in the development of this disorder, although it must certainly play some part in the formation of the renal calcification and urinary tract stone that so often complicates this disease.[24]

Thus, in renal tubular acidosis nature has prepared an experiment for the perceptive observer. Here is a fascinating revelation of the interplay of certain physiologic, biochemical, and genetic factors and of their bearing on the clinical course of the patient. In these circumstances, exploration of these many factors will subserve a greater purpose than that of satisfying the intellectual curiosity of the explorer. The understanding so obtained may permit the physician to restore and maintain the health of the person who after all is the one most intimately concerned, the one who plays unwilling host to this experiment of nature, the patient.

J. R. E.
E. J. H.

THE SYNDROME OF INTRATHORACIC NEOPLASIA WITH BILATERAL HYPERFUNCTION OF THE ADRENAL CORTEX *

ELSEWHERE in this issue [1, 2] are reported two further instances of a striking and as yet imperfectly understood association between intrathoracic neoplasms and adrenal cortical hyperplasia and hyperfunction. Such an association, occasionally noticed from time to time in the past, is now being recorded with such frequency as to leave no doubt that the coexistence of these two disease processes is more than fortuitous. It is time to take stock of this syndrome both in the interest of the diagnostician and because of its intrinsic interest from the standpoint of pathophysiology.

To date 30 case reports [1-11] have appeared in the literature documenting

[24] Harrison, H. E., Harrison, H. C.: Inhibition of urine citrate excretion and the production of renal calcinosis in the rat by acetazoleamide (Diamox®) administration. J. Clin. Invest. **34**: 1662, 1955.

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[6] Bornstein, P., Nolan, J. P., Bernanke, D.: Adrenocortical hyperfunction in association

the association of hyperadrenocorticism with pulmonary neoplasms. In addition, three cases have been reviewed [12] and nine others have been mentioned, in each of which hyperadrenocorticism was associated with an intrathoracic neoplasm of thymic origin. The association of hyperadrenocorticism with miscellaneous extrathoracic, extra-adrenal neoplasms has also been recorded from time to time.[3] These latter neoplasms, however, with the possible exception of those of the pancreas, are quite heterogeneous and may be suspected of representing diseases associated by chance, and we shall here confine our attention to the intrathoracic neoplasms; these seem to constitute a homogeneous group comprising by far the majority of extra-adrenal neoplasms coexisting with hyperadrenocorticism.

The guise in which hyperadrenocorticism presents itself, when associated with an intrathoracic neoplasm, exhibits some peculiarities compared with the more common hypercortisolism due to bilateral adrenal cortical hyperfunction. A large number of the patients with intrathoracic neoplasms had no clinical manifestations of Cushing's syndrome, although chemical and anatomic evidence indicating hyperadrenocorticism was present. The patients harboring intrathoracic neoplasms have usually been middle-aged males rather than the young females who are especially afflicted with hypercortisolism. The clinical hyperadrenocorticism has frequently been acute in onset and fulminant in course, and severe hypokalemic alkalosis has been the rule rather than the exception.

The alkalosis and potassium depletion may suggest primary aldosteronism, but in all but one [13] of the few cases in which the aldosterone content of urine or adrenal glands has been measured, low values have been reported. It should be borne in mind, however, that low values for urinary aldosterone are common enough in severely potassium-depleted patients harboring an aldosteronoma. The quantity of 17-ketosteroids, 17-ketogenic steroids, and 17-hydroxycorticosteroids excreted in the urine per 24 hours, and the concentration of the latter in the plasma, have consistently been markedly elevated, often to a greater level than is ordinarily encountered in Cushing's syndrome due to bilateral adrenal cortical hyperfunction (Table 1). It is

with anaplastic carcinoma of the respiratory tract. New Engl. J. Med. **264**: 363–71 (Feb.) 1961.

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TABLE 1

Evaluation of Pituitary-Adrenal Axis in Hyperadrenocorticism Associated with Pulmonary Neoplasms

Author	Steroid Determinations	Resting Levels	Corticotrophin Stimulation	Corticotrophin Suppression
Metzler and Flink[11]	Urine 17-hydroxycorticosteroids (in mg. per 24 hr.)	78.4, 84.3, 90.7, 71.7	Not performed	9 α-fluorohydrocortisone, 1 mg. q.i.d. by mouth for 2 days 53.6, 37.1
Harrison et al.[7]	Urine 17-ketogenic steroids	Reported as normal	6-day corticotrophin stimulation No response	Not performed
	Urine 17-ketosteroids	Reported as normal	Normal response	Not performed
Rosenthal[8]	Urine 17-ketosteroids	50.4	ACTH, 25 mg. q.6 hr. I.M. for 48 hr. No response	Cortisone, 50 mg. q.6 hr. by mouth for 48 hrs. No response
	Urine 17-ketogenic steroids	138.0	No response	No response
Allott and Skelton[3] (Case 2)	Urine 17-ketosteroids	15.2	Not performed	9 α-fluorohydrocortisone, 5 mg. q.i.d. for 4 days No response
	Urine 17-hydroxycorticosteroids	136.0	Not performed	No response
Christy[6] (Case A.B.)	Plasma 17-hydroxycorticosteroids (in μg. %)	115.0–120.0	No response	Not performed
(Case B.C.)	Plasma 17-hydroxycorticosteroids (in μg. %)	43.0	80.0	Not performed
Escovitz and Reingold[1]	Urine 17-ketosteroids (in mg. per 24 hr.)	45.6	ACTH, 40 mg. q.8 hr. I.M. for 4 days 3rd day = 56.0, 4th day = 59.0	4th day of Florinef acetate, 0.5 mg. b.i.d. by mouth, 50.0
	Urine 17-ketogenic steroids (in mg. per 24 hr.)	32.6	3rd day = 47.0, 4th day = 117.0	11.0
Marks et al.[2*]	Plasma free 17-hydroxycorticosteroids (in μg. %)	18.0	ACTH, 30 units I.V. over 6 hr. 93.0	Not performed
	Plasma conjugated 17-hydroxycorticosteroids (in μg. %)	7.0	42.0	Not performed

* Adrenal cortical hyperplasia without evidence of clinical hyperfunction.

entirely possible that the severe electrolyte disturbance is a reflection of the extreme elevation of cortisol production.[14] It is noteworthy that markedly elevated urinary 17-ketosteroid excretion has been regarded as a sign that an adrenal cancer, rather than bilaterally hyperfunctioning cortices, is likely to underlie the Cushing's syndrome.

It may be that, in many cases of this syndrome, dependence upon and responsiveness to corticotrophin may be absent or at least less prominent than that seen in simple bilateral adrenal cortical hyperfunction. Unfortunately, in the limited number of cases which have been studied by stimulation or suppression tests, a variety of procedures has been used and no firm inferences seem warrantable (Table 1). It would be valuable if future cases could be studied by standard technics of corticotrophin suppression and stimulation for which extensive data in Cushing's syndrome have been collected. Probably the most suitable procedures according to these criteria are the dexamethasone suppression test at two dose levels, as proposed by Liddle [15] and the use of ACTH intravenously, 20 units over eight hours, on one or several successive days, with measurement of urinary 17-ketosteroids and 17-hydroxycorticosteroids per 24 hours on control and infusion days.

The intrathoracic neoplasms also have had certain distinguishing features. The pulmonary cancers have been, almost without exception, of the small oat-cell variety, which is the least common of the four histologic types of bronchogenic carcinoma.[16] In addition, two bronchial adenomas and nine thymomas associated with clinical Cushing's syndrome were histologically atypical, and their cellular structure was reminiscent of that of oat-cell carcinomas.[10] The tendency to a uniform microscopic appearance of these tumors may be the histologic expression of a particular secretory activity common to them (see below).

In the vast majority of reports, the adrenal glands exhibited cortical hyperplasia with proliferation of the zona fasciculata and zona reticularis and occasionally a tendency to adenoma formation. The zona glomerulosa was often recorded as atrophic. In several cases, however, the zonal architecture was obliterated. Metastatic deposits were not consistently present. As pointed out by Bornstein et al.,[6] these glands usually weighed significantly more than those found in Cushing's syndrome due to bilateral adrenal cortical hyperfunction without concomitant carcinoma, even when metastatic deposits were taken into account. Pituitary metastases were occasionally noted but the glands were otherwise normal.

The association between hyperadrenocorticism and intrathoracic neo-

[14] Sprague, R. G., Power, M. H., Mason, H. L., Albert, A., Mathieson, D. R., Hench, P. S., Kendall, E. C., Slocumb, C. H., Polley, H. F.: Observations on the physiologic effects of cortisone and ACTH in man. Arch. Intern. Med. **85**: 199–258 (Feb.) 1950.

[15] Liddle, W. G.: Tests of pituitary-adrenal suppressibility in the diagnosis of Cushing's syndrome. J. Clin. Endocr. **20**: 1539–60 (Dec.) 1960.

[16] Moersch, H. J., McDonald, J. R.: The significance of cell types in bronchogenic carcinoma. Dis. Chest **23**: 621–33 (June) 1953.

plasms appears to constitute a distinct nosologic entity, but the mechanism by which these two disease processes are linked has not been elucidated. Usually it is impossible to ascertain in the individual case whether the neoplasm antedated the hyperadrenocorticism, or vice versa. But it is hardly to be supposed that the hyperadrenocorticism gives rise to the neoplasms. Extensive experience with severe and long-standing hypercortisolism, spontaneous as well as iatrogenic, has failed to implicate extra-adrenal neoplasia as one of its sequelae. Moreover, the clinically short duration of the hyperadrenocorticism and the frequent absence of Crooke's hyaline changes in the pituitary of patients with this syndrome [3] support the view that the development of the neoplasm antedates or accompanies the appearance of the endocrine abnormality.

That the adrenal cortex is itself overactive can hardly be doubted, in view of the conjunction of excessive levels of cortical hormone in blood and urine with gross and histologic evidence of hyperplasia of the cortices; and it therefore is most unlikely that the neoplasms are themselves secreting cortical hormones, although this possibility has not been directly excluded. It is more likely, indeed highly probable, that the neoplasms secrete a material which results directly or indirectly in continuous overstimulation of the cortices. It seems that the two principal possibilities are that the neoplasms may secrete (1) conventional corticotrophin (or a substance with similar activity); (2) a substance which directly or indirectly results in excessive release of corticotrophin from the adenohypophysis. In only one case thus far has an attempt to gain direct evidence on this point been recorded: Bagshawe [4] assayed a cervical node containing anaplastic metastases from primary bronchial or thymic elements for corticotrophic activity, but could detect none. Christy [5] detected adrenal weight-maintaining activity in the plasma of two patients with this syndrome and proposed to determine whether pituitary irradiation could cause it to disappear. In this connection an alternative hormonal role for the neoplasms could be considered, namely, that they might elaborate a material such as the postulated "adrenal weight factor," [17, 18] which might increase the sensitiveness of the cortices to conventional corticotrophin. However, it is difficult to conceive how such a factor could cause severe hyperadrenocorticism unless the regulatory function of the adenohypophysis in the pituitary-adrenal cybernetic system had also been damaged or lost. It appears possible that conventional corticotrophin might account for adrenal weight-maintaining activity in the system employed.[19] Recently Bornstein et al.[6] reported excessive cortico-

[17] Liddle, G. W., Island, D. P., Rinfret, A. P., Forsham, P. H.: Factors enhancing the response of the human adrenal to corticotropin: is there an adrenal growth factor? J. Clin. Endocr. **14**: 839–58 (Aug.) 1954.

[18] Jailer, J. W., Longson, D., Christy, N. P.: Studies in Cushing's syndrome. II. Adrenal weight-maintaining activity in the plasma of patients with Cushing's syndrome. J. Clin. Invest. **36**: 1608–14 (Nov.) 1957.

[19] Nugent, C. A., Eik-Nes, K., Kent, H. S., Samuels, L. T., Tyler, F. H.: A possible explanation for Cushing's syndrome associated with adrenal hyperplasia. J. Clin. Endocr. **20**: 1259–68 (Sept.) 1960.

trophic activity in the plasma of their patient employing the rat adrenal vein corticosterone bio-assay method.[20]

The existence of this syndrome obliges the physician to be alert to the possibility of adrenal cortical overactivity (often clinically masked) in patients harboring neoplasms; and to suspect a neoplasm, especially intrathoracic, in any case of Cushing's syndrome with bilaterally hyperfunctioning adrenals which occurs in a mature male, is abrupt in onset or rapidly becomes severe, or is accompanied by severe hypokalemic alkalosis or very high urinary excretion of 17-hydroxycorticosteroids and 17-ketosteroids. Physicians who have patients with this syndrome under their care may have an unique opportunity to elucidate the pathogenesis of the condition if it is possible to submit neoplastic tissue, fresh or quick-frozen, to thoroughgoing chemical analysis, including assay for corticotrophic activity by sensitive new methods [20] and for steroid content by chromatography. Detailed analysis of steroids present in the hyperplastic adrenal cortices would also be of great interest. It might be rewarding as well to attempt tissue culture growth of these neoplastic cells, and to devise an assay for a substance, which they might elaborate, which would result directly or indirectly in greatly enhanced secretion of corticotrophin by the pituitary. The seemingly bizarre association of cortical hyperfunction and intrathoracic tumors provides another point of intersection of unsolved problems of neoplasia with endocrine function and dysfunction, and may repay thorough study generously and in ways which we can by no means at the moment clearly foresee.

A. Gorman Hills, M.D.,
Kenneth A. Woeber, M.B., Ch.B.

THE ABUNDANT LIFE

Mens sana in corpore sano—a sound mind in a healthy body—is the goal of our endeavors as physicians, for ourselves as well as for our patients. The paths to this goal are usually harder to see than the goal itself; the literature of the world is replete with recipes for happiness. And not only are the methods of procedure many but the goal itself is varied. In earlier days and in primitive societies the chief objective used to be just to stay alive; a recent cartoon in the *Saturday Review* shows a native against a background of Floridian swamp and alligators, responding to Ponce de Leon, "Fountain of Youth? Around here we feel it's a real privilege to reach middle age." Today even the native has his eye on the fringe benefits.

Two papers in this issue illustrate the diversity of methods of attempting to achieve the fringe benefits. Now that more and more of us stay alive until middle age and beyond, more attention must be paid to maintaining the *mens sana in corpore sano* of the expanding older population. Dr. Raab

[20] Williams, W. C., Jr., Oldfield, R. A. A., Jr., Island, D. P., Liddle, G. W.: Blood ACTH in Cushing's disease. J. Clin. Invest. 39: 1040, 1960.

suggests that the middle-aged working population of the United States might well benefit from the use of organized reconditioning centers, as initiated in Germany and as now practiced in Continental Europe. If such a program could achieve a higher level of health for a greater number of people, it should be given serious consideration. Platoons of pot-bellied older citizens in a state of undress doing calisthenics in meadows studded with buttercups may seem a bit regimented to the American eye. But it is undoubtedly more healthy than the negative activities of most spectator sports, including that of watching the little black box in the living room. Another approach to the *corporo sano* is that of Dr. Clark and his colleagues, who report on results of a large scale program of periodic health examinations. This study, which highlights some of the limitations as well as the advantages of this preventive medical approach to middle-aged health, is certainly more in the American tradition.

But there are many roads to the sound mind in a healthy body, to the abundant life, that may be explored by patient and physician. Each of us has his own individual formula for reconditioning, each his own recreative avocations, whether in field and stream, on lake and mountain, on beach or sea. As for the Editor, he knows of a quiet lake, a remote forest, a strong canoe, and some reluctant fish—but not until the next issue is off to press!

J. R. E.

BOOK REVIEWS

The Great Epidemic. By A. A. HOEHLING. 217 pages; 21 × 14 cm. Little, Brown and Company, Boston, 1961. Price, $3.95.

The world-wide spread of influenza in 1918 well deserved to be named "The Great Epidemic"; in this country alone some twenty million persons were sickened and over five hundred thousand died. It disrupted every phase of daily life, and slowed up our war effort here and abroad. The fact that the cause was unknown and that no specific therapy was available increased the tendency to panic and hysteria. The resulting situation, well described in this book, must seem incredible to the present generation who have been lulled to believe that no such epidemic can ever happen again.

This volume is described on its cover as a "dramatic documentary," and this it certainly is. The author has quoted from many newspapers and personal interviews; the result is a unique collection of contemporary data. Of course the more spectacular material is given preference, and because of this and some repetition, the picture as a whole is over-dramatized, but it is the documentation that makes the volume of lasting value as source material.

As this review is for a medical journal it must pay special attention to criticizing the sections dealing with the epidemiology, bacteriology, pathology, and clinical features of the disease. These obviously presented difficulties for a lay author; the result is that there is too much material on these subjects for the lay reader, while the medical man will find much to criticize. It is difficult to discuss scientific matters in a book written in popular style. Minor errors alert the reader for others; on page 5, for example, occurs the florid sentence, "A celebrated research physician of London, remembered only as 'Dr. Willis,' in 1658 described influenza's calling cards. . . ." This reviewer suspects that this was Thomas Willis who, although his name is attached to the *circulus arteriosus,* was scarcely a celebrated research physician.

To illustrate the wide-spread efforts to discover the cause of influenza the author chose to trace the efforts of a single researcher who unfortunately came to the erroneous conclusion that it was due to Pfeiffer bacillus. Nor will the doctors who did their best to fight the epidemic fail to be irritated at the emphasis placed on their helplessness, implying that they had no more to offer in 1918 than had their predecessors in London in the plague of 1665. Little mention is made of the segregation of "clean" cases from those with streptococci in their throats, nor of the many lives which were saved by repeated removal of recurring massive pleural effusions.

The author records many of the crackpot suggestions offered for the prevention and cure of influenza, and seems to prefer those advanced by doctors, perhaps to hint that they were turning in their ignorance to folk medicine and such absurdities as diphtheria antitoxin as a specific.

Read this book for the general documentary material, but not for the medical aspects of the epidemic.

O. H. PERRY PEPPER, M.D.

Systemic Lupus Erythematosus. By DANIEL L. LARSON, M.D. 212 pages; 21.5 × 14.5 cm. Little, Brown and Company, Boston, 1961. Price, $7.50.

Systemic Lupus Erythematosus presents a series of clinical observations made on two hundred patients who were seen during the past twenty years at New York Presbyterian Hospital. Some of the observations were made directly by the author and many were obtained from analyses of hospital charts.

In picking up a book boldly titled *Systemic Lupus Erythematosus* in which is stated, "The following monograph is a review of our current knowledge of clinical, laboratory and pathological features of systemic lupus erythematosus," one expects to find a more complete analysis of the disease than that which is presented. The data are accurate and largely clinical, but the book shows no significant effort to correlate the findings of the author, and his records, with those of other workers. Descriptive data are at times complete, yet, at other times, superficial, as in the section on cutaneous features. The coverage of renal involvement is too brief for an aspect of the disease that affects survival so strikingly. Although the proper therapy for renal systemic lupus erythematosus is an unsettled matter, there is much more evidence available for evaluation than is presented.

The case reports and tables are well done throughout; hence very valuable data have been added to the literature on this disease. The general format and indexing are good, and the bibliography covers much of the pertinent literature on the clinical aspects of this disease.

In brief, the clinical analyses of hospital records of two hundred patients with systemic lupus erythematosus are presented well, with no attempt made to review the disease in detail. In limiting the scope of the presentation Doctor Larson may have attempted to keep the subject sufficiently brief to allow for easy reading. However, this type of short cut is more acceptable in a medical journal article than in a book that might have presented a more searching analysis of a fascinating subject.

EUGENE A. HILDRETH, M.D.

Dermatology, Diagnosis and Treatment. By MARION B. SULZBERGER, M.D., F.A.C.P., JACK WOLF, M.D., and VICTOR H. WITTEN, M.D., with the collaboration of ALFRED W. KOPF, M.D. 615 pages; 23 × 15.5 cm. The Year Book Publishers, Inc., Chicago, Ill., 1961.

This book represents the third in a series of volumes prepared by Sulzberger and one or more of the above co-authors on the diagnosis and management of the most common skin diseases. Previous efforts appeared under slightly different titles, viz., *Dermatologic Therapy in General Practice,* which had three editions, and *Dermatology, Essentials of Diagnosis and Treatment.*

Although the material has been rewritten and modernized, the general format of this book is only slightly changed from that of the earlier publications listed above. A new chapter on pruritus, a comprehensive consideration of the current use of topical and systemic antibiotics and corticosteroids in dermatology, and deletion of the chapters on syphilis represent the major changes. The chapters dealing with the eczematous dermatoses, fungal infections (including a discussion of the uses of griseofulvin and mycostatin), and that on drug eruptions are worthy of special citation.

This book, like its predecessors, is designed primarily for the non-dermatologist, from medical student to practicing physician. It is a storehouse of practical information and its special attractiveness lies in the meticulous attention given to the fine points of dermatologic care, so often neglected in the average text on skin diseases. A thorough discussion of the precise use, mode of application, and the special problems or contraindications for the various forms of therapy is presented. Nowhere else in the field of dermatology is such a detailed and lucid consideration of these measures to be found. One could be critical only of the inclusion in some chapters of empirical therapy of highly questionable value.

Technically the book is well done. The typography is excellent and the illustrations, highlighted by twelve color plates, are for the most part outstanding. Selected references are conveniently placed at the bottom of the page on which related material has been discussed.

All physicians without broad dermatologic experience who are faced with the

task of managing skin disorders will find this book of inestimable value. For these physicians especially, but also for all interested in dermatology, it is highly recommended.

HARRY J. HURLEY, M.D.

Pharmacology. The Nature, Action and Use of Drugs. 2nd Ed. By HARRY BECKMAN, M.D. 805 pages; 26 × 18.5 cm. W. B. Saunders Company, Philadelphia, 1961. Price, $15.50.

The arrangement of the topics in this work is different from that in the usual textbook of pharmacology. The chapters are labeled according to the primary clinical use of the drug. Thus digitalis is discussed in the chapter on drugs that stimulate cardiac muscle and quinidine in the chapter on depressants. Both appear in the section entitled "The Pharmacology of Muscle."

The autonomic drugs which affect blood pressure appear in two sections dealing with the pharmacology of the blood vessels and the pharmacology of the autonomic nervous system. The latter includes the major discussion of the sympathomimetic drugs, whereas the former discusses the hypotensive agents which block the autonomic nervous system. Such an arrangement may be confusing to the hurried reader who habitually looks at the table of contents to find a drug, rather than at the index. On the other hand, the author should be congratulated on offering a complete classification based on the clinical use of drugs which are presently available as well as those which will be introduced.

The physician will be pleased to know that this book is the latest revision of the several textbooks of pharmacology used in American medical schools. The book can be highly recommended as a reference for cardiovascular drugs, including those introduced during the past year. Bretylium, a new form of antihypertensive agent which blocks sympathetic nerves, is included.

DOMINGO M. AVIADO, M.D.

Clinical Pharmacology. By D. R. LAURENCE, M.D., M.R.C.P., and R. MOULTON, M.D. 490 pages; 21 × 14 cm. Little, Brown and Company, Boston, 1960. Price, $10.00.

The opening chapters, "Drug Therapy, Placebos and Tonics," and "Development of New Drugs, Therapeutic Trials," are the best discussions of these topics that the reviewer has read. They are both brief and straight to the point, and this is true for the twenty-seven succeeding chapters. The use of British names and terms for drugs (like local analgesics) may annoy some American readers but confusion is very unlikely. The book is full of direct quotations, because the authors feel that where a point has been well made by an original observer or thinker, there are excellent reasons for not imposing the mind of another. In this spirit, the reviewer would like to quote the authors' own opening paragraphs in their preface: "This book is intended primarily for medical students in their clinical years and for those newly qualified, but it is hoped that this survey of the principal drugs, with details of their use and pharmacology, may be helpful to some postgraduate students and general practitioners.

"Most books of moderate size confine themselves either to discussing the pharmacology of drugs without giving enough information for them to be selected and used effectively, or else they confine themselves to practical therapeutics and ignore the pharmacological background, without which efficient use of many drugs is difficult, or even impossible. It is nowadays too much to expect the heavily overburdened student to consult and integrate two works, one not always clearly related to clinical practice and the other often as arbitrary, and as apparently empirical, as a cookery

book. This book is offered as a reasonably brief solution to the problem of combining practical clinical utility with some account of pharmacology."

DOMINGO M. AVIADO, M.D.

Review of Medical Microbiology. 4th Ed. By ERNEST JAWETZ, M.D., JOSEPH MELNICK, M.D., and EDWARD A. ADELBERG, Ph.D. 376 pages. Lange Medical Publications, Los Altos, Calif., 1960. Price, $5.00.

The authors' purpose is to provide a brief, accurate presentation of the aspects of medical microbiology which are significant in the field of clinical infections and chemotherapy. The book encompasses in 377 pages the basic science of medical microbiology. It includes brief but accurate descriptions of bacterial classification, cytology, metabolism, variation, and methods. There are discussions of environmental bacteriology, immunology and allergy, characteristics of different genera of bacteria, as well as the rickettsiae, viruses, and fungi. References are few and are limited to one page.

Exceptions to general statements and detailed discussion are omitted. The review should not be used as a text for the beginning student in medical bacteriology for it is too compact and brief. Medical students and physicians who have a background of knowledge and experience will find it excellent for review and reference.

The authors are well qualified to prepare this book. Dr. Jawetz, the senior author, is a physician and microbiologist with clinical, research, and teaching experience. The book is revised every two years.

ROBERT I. WISE, M.D.

Pseudemonas Aeruginosa Infections. By CLAUDE E. FORKNER, JR., M.D. 73 pages; 23 × 14.5 cm. Grune & Stratton, New York, 1960. Price, $5.25.

This compact monograph presents an extensive review of the clinical manifestations of pseudomonas infections. Since superinfections with *Ps. aeruginosa* are a more frequently observed complication of both medical and surgical problems, this review points up for the clinician features which place this organism in perspective as an annoying and resistant pathogen.

The contents include, in addition to clinical features, a presentation of bacteriologic and immunologic characteristics, antibiotic therapy, and pathology of *Ps. aeruginosa.* None of these chapters are as lengthy or as comprehensive as the clinical manifestations. Therapy includes a description of the activity of colistin esters as well as polymyxin B; a more critical evaluation of this phase of clinical management would be welcomed.

A bibliography of 465 references will give the reader ample opportunity to increase his background on these infections.

Its greatest usefulness will be found in delineating for the clinician the various clinical manifestations of pseudomonas infections which have been observed in practically every organ and system of the body.

E. L. FOLTZ, M.D.

Clinical Use of Radioisotopes: A Manual of Technique. 2nd Ed. Edited by THEODORE FIELDS, M.S., F.A.C.R. (Assoc.) and LINDON SEED, M.D., with 18 contributors. 475 pages; 19.5 × 13 cm. The Year Book Publishers, Inc., Chicago. 1961. Price, $10.50.

The high level of activity in the field of clinical radioisotopes has resulted in a large volume of printed material appearing in almost every medical journal available.

It is, therefore, very helpful to have a text which "boils down" all this material and presents in step by step fashion the radioisotope techniques of proven value and the interpretation of results obtained.

Part I, "Routine Clinical Diagnostic Tests," describes the techniques used for thyroid evaluation, blood volume measurement, red cell volume and survival time determinations, vitamin B_{12} absorption tests, tumor localization procedures, peripheral vascular and cardiac output studies, fat absorption measurements, liver function tests, radioautography preparations, and scanning procedures. Part II, "Routine Clinical Therapy Technique," describes the methods used in treating toxic goiter, polycythemia vera, leukemia, cancer of the thyroid, malignant effusions, carcinoma of the prostate, myocardial and coronary insufficiency, skin, mucous membrane, and eye lesions. Part III, "Planning and Operating the Radioisotope Laboratory," provides a review of the history and physics of the clinical use of isotopes. It discusses the needs of the laboratory, the radioactive materials available for medical use, and the instrumentation used. Part IV, "Radiation Safety," is devoted to recommendations for reducing the health hazards of this work, instructions to laboratory personnel for preventing unnecessary radiation exposure, and instructions to hospital personnel for handling patients who have received radioisotopes.

In the process of "boiling down" the voluminous literature on clinical radioisotopes, the authors seem to have lost a few "volatile" isotope procedures of importance. No mention is made of any of the radioactive iron techniques in the measurement of erythrokinetics. Also omitted is the use of chromium-^{51} tagged red cells in the determination of intestinal bleeding. In the section on fat absorption, the authors describe only blood curves and do not describe stool measurements which are equally if not more significant. The inclusion among isotope dilution techniques of sections on chromium-^{51} survival studies and radioactive vitamin B_{12} diagnostic tests represents poor organization.

To the average internist an isotope technique manual will be of little value. A book encompassing all known techniques, their general principles, selection of the appropriate one, their interpretation and follow-up would be of greater value to him. However, to the physician who has been selected to set up an isotope laboratory for the hospital, the book will be of real assistance.

BERNARD SHAPIRO, M.D.

Radioisotope Laboratory Techniques. 2nd Ed. By R. A. FAIRES and B. H. PARKS. 236 pages; 22 × 14.5 cm. Pitman Publishing Corp., New York, 1960. Price, $5.75.

This small volume is an introduction to the use of radioisotopes for biochemists and other laboratory workers, written by staff members of the Isotope School, Atomic Energy Research Establishment, Harwell, England. It opens with a section on nuclear physics which is perhaps too condensed to be effective for the reader who lacks previous knowledge of the field, but which would serve as an excellent review for the initiated. The bulk of the book is devoted to descriptions of radioisotope laboratory apparatus and its use, including some elements of electronics, radiation physics, and such practical matters as sample preparation and the statistics of counting. There is an introduction to health physics, and a brief discussion of autoradiography. A ten-page appendix provides some tables of useful physical constants, although of course the coverage of physical data useful in isotope work is far from complete in this space.

The material in the book is well presented, and shows abundant evidence of the authors' wide experience in teaching the subject. American readers may find the British accent a little less charming in print than it is to the ear, since some terms

such as "outhouse" and "fume-cupboard" may require translation. The paper and printing are good, and the index is fair. The illustrations of laboratory equipment will be especially valuable to readers unfamiliar with the multiplicity of available apparatus.

The biggest drawback for readers in the United States is the fact that, naturally enough, no mention is made of the U. S. Atomic Energy Commission safety regulations nor of the radiation safety requirements of the individual states. Since these are in general somewhat more specific than are the recommendations in this volume, readers using this book as a guide might fail to recognize some of their safety obligations in handling radioisotopes.

The reviewer feels that the book will be most useful as a text for an organized course in radioisotope laboratory technique, or as supplementary reading for laboratory workers who have a general library on the subject; but it should not be the sole reference for an American scientific worker previously untrained in the use of radioisotopes.

ANTOLIN RAVENTOS, M.D.

The Conquest of Pain. By RONALD WOOLMER, M.D. 240 pages; 22 × 15 cm. Alfred A. Knopf, Inc., New York, 1961. Price, $4.50.

The jacket of this book accurately states that it provides "a clear description for the general reader of how modern medicine has developed new anesthetic techniques that make possible operations unthinkable only a few years ago." Since the book is addressed to the general reader it will not, in my opinion, appeal to a reader possessing medical training. Because modern anesthesia may seriously interfere with the normal working of heart, lungs, and so on, the book describes pertinent aspects of the physiology and pathology of these organs. There are also chapters on blood transfusion, drug addiction, and pharmacologic research.

The author is well qualified to write such a book, and he has written it well. There are five instances in which the author's scientific statements might be challenged, but these differences of opinion would not be of interest to the general reader. The excellent indices (hardly necessary in a book of this nature) could be copied to advantage by other authors. The publishers have done a good job, too.

AUSTIN LAMONT, M.D.

BOOK NOTICES

Handbook of Medical Treatment. 7th Ed. Edited by MILTON J. CHATTON, M.D., SHELDON MARGEN, M.A., M.D., and HENRY BRAINERD, M.D. 572 pages; 17 × 10 cm. Lange Medical Publications, Los Altos, Calif., 1960. Price, $3.50.

This pocket sized handbook gives specific instructions for the immediate treatment of practically any disease that the physician might encounter. Drugs are specified, both by generic and by trade names, and an average dosage schedule is outlined. The advantages and disadvantages of the various procedures are stated, and side effects or contraindications are listed. The printing is easily legible and the index seems to be complete.

This book should prove to be very helpful to interns and residents; it offers the practicing physician a reliable source of information concerning the management of diseases which he may encounter only at rare intervals in his daily practice.

HENRY HOPKINS, M.D.

Advances in Blood Grouping. By ALEXANDER S. WIENER, M.D., F.A.C.P. 549 pages; 26 × 17.5 cm. Grune & Stratton, New York and London, 1961. Price, $11.00.

Fifty-seven papers and shorter contributions by Dr. Wiener and his co-authors have been reproduced by the photo offset process and assembled under various topical headings. The main topics covered are the blood types (A-B-O and Rh-Hr systems), hemolytic disease, blood transfusions, medicolegal applications of blood grouping, and nomenclature of blood groups. These papers originally appeared in journals between 1946 and 1960.

For this collection Dr. Wiener has written a preface. Following the text is a list of Dr. Wiener's papers which were published in the years 1953 to 1960. Author and subject indices have been prepared.

EDWARD J. HUTH, M.D.

L'Enfisema Polmonare: Fisiopatologia, Clinica e Terapia. By EMILIO SARTORELLI, MAX MAGISTRETTI, and ANTONIO GRIECO. 184 pages; 24 × 17 cm. Edizioni Minerva Medica S. A., Torino, Italy, 1960. Price, L 4000.

This Italian monograph presents the findings of a physiologic, clinical, and therapeutic study of four hundred fifty-three patients with pulmonary emphysema who were seen at the Clinic for Occupational Medicine, Milan, between 1950 and 1959. Summaries in English, French, and German are given following the Italian text. An extensive bibliography is drawn from the American and European literature.

EDWARD J. HUTH, M.D.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. So far as is practicable those of special interest will be reviewed, but it is not possible to discuss them all.

The Atoms within Us. By ERNEST BOREK. 272 pages; 22.3 × 14.5 cm. Columbia University Press, New York, 1961. Price, $5.00.

Clinical Pharmacology. By D. R. LAURENCE, M.D., M.R.C.P., and R. MOULTON, M.D. 490 pages; 21 × 14 cm. Little, Brown and Company, Boston, 1960. Price. $10.00.

The Conquest of Pain. By RONALD WOOLMER, M.D. 240 pages; 22 × 15 cm. Alfred A. Knopf, Inc., New York, 1961. Price, $4.50.

The Couch and the Circle: A Story of Group Psychotherapy. By HYMAN SPOTNITZ, M.D., MED. SC. D. 274 pages; 22 × 15 cm. Alfred A. Knopf, Inc., New York, 1961. Price, $4.50.

Diagnostic Stomatology: A Clinical Pathologic Approach. By E. CHERASKIN, M.D., D.M.D. 338 pages; 24 × 15.5 cm. McGraw-Hill Book Company, Inc., New York, 1961. Price, $12.50.

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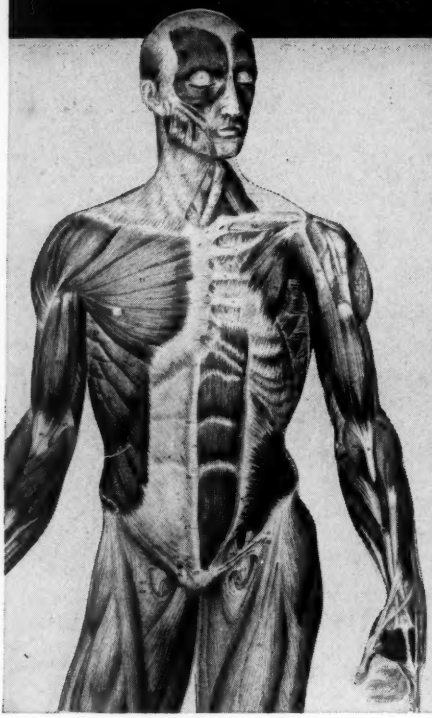
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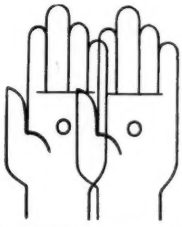
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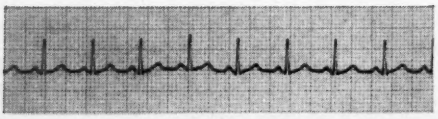
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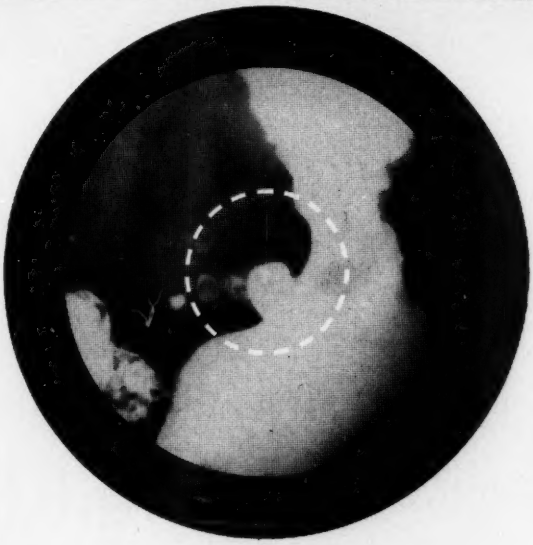
Perhaps they do . . . if you consider their "tools" to be only soldering irons, spare components, milliammeters and the like. But what about their training, experience, and personal interest in your satisfaction?

The men who service Sanborn electrocardiographs are qualified technicians — highly skilled and experienced in medical electronics. Their training and experience are important; but important, too, is their direct, personal interest in providing every Sanborn owner with competent, prompt, responsible service.

It's a "service tool" well worth remembering the next time you buy an electrocardiograph.



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INDICATED:

THE PAIN-RELIEVING ANTACID WITH

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Only Gelusil provides prompt and lasting acid neutralization plus the protection of two demulcent coating gels to relieve ulcer pain promptly. Gelusil promotes the natural healing process -- is inherently nonconstipating -- contains no laxative. These qualities make pleasant-tasting Gelusil the superior antacid adjuvant for any program of management in peptic ulcer, gastritis or hyperacidity.

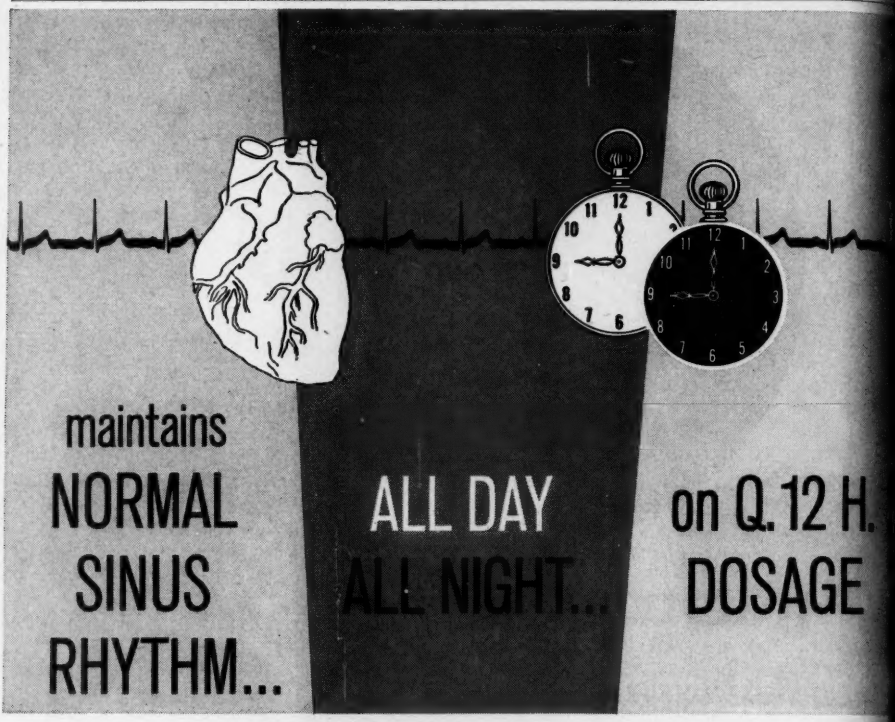
Available in tablet and liquid forms; each tablet or teaspoonful contains aluminum hydroxide (Warner-Chilcott) 4 gr. and magnesium trisilicate U.S.P. 7½ gr.

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IN CARDIAC ARRHYTHMIAS[1-10]

Maximum efficacy: maintains effective quinidine blood levels all day, all night. **Bet tolerated:** because quinidine gluconate is 10 times as soluble as the sulfate, and on part of daily Dura-Tab dosage contacts gastric mucosa. **Maximum convenience:** giv q. 12 h.—no night dosage needed.

DOSAGE: for conversion of auricular fibrillation to normal sinus rhythm, in most cases, 2 Dura-Ta 3 or 4 times a day, for 2 to 3 days; longer periods are required in some patients. **For maintena** 2 Dura-Tabs q. 12 h. in most patients... Bottles of 30, 100 and 250 Quinaglute Dura-Tabs.

For SAMPLES and complete literature[1-10] giving indications, cautions, etc., write

REFER TO PDR Page 821

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TWO SPECIFIC ACTIONS • FEWER SIDE REACTIONS New Tigacol facilitates the symptomatic control of vertigo. It relieves the varied symptoms of vertigo whether due to labyrinthitis, Meniere's syndrome, impaired cerebral circulation or of nonspecific origin. Tigacol offers you the clinically proven advantages of a well-tolerated peripheral vasodilator and a new specific antiemetic. **Roniacol** promptly relieves vertigo by directly relaxing the peripheral blood vessels without causing severe flushing or hypotension. **Tigan** controls nausea and vomiting by selective suppression of emetic impulses without drowsiness, tranquilization or adrenergic effects.

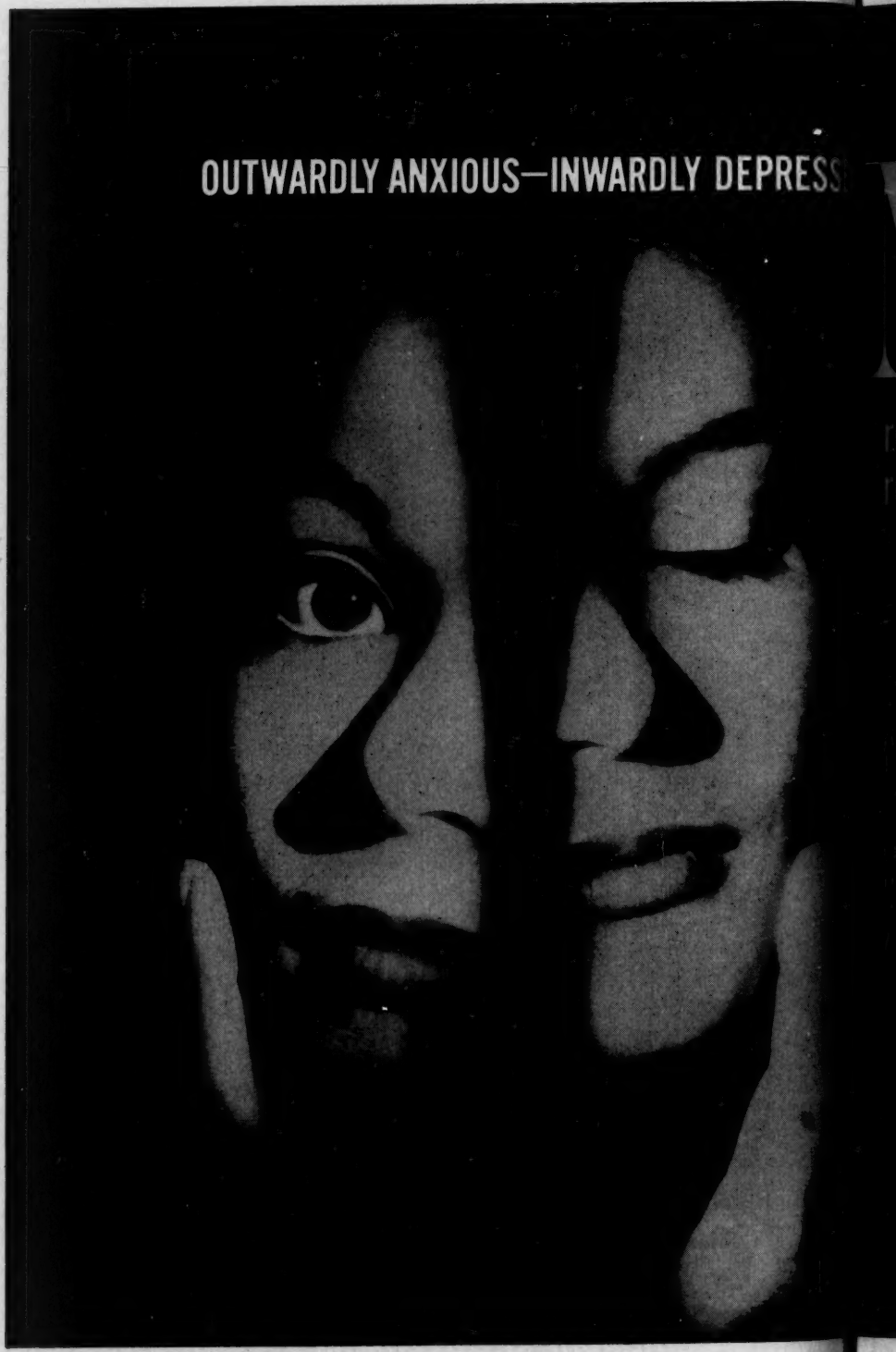
AVAILABLE: Pink capsules, each providing 50 mg Roniacol in the form of the tartrate and 100 mg Tigan HCl, bottles of 50. **USUAL ADULT DOSAGE:** One or two capsules three times daily. **NOTE:** Side effects were virtually absent except for a few instances of vomiting and an occasional case of skin rash, which disappeared when medication was withdrawn. There are no known contraindications, but as with any new drug, patients should be observed periodically while on Tigacol therapy.

Roniacol®—brand of nicotinyl alcohol • Tigan®—4 (2 dimethylaminoethoxy) N (3,4,5 trimethoxybenzoyl)benzylamine

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TIGACOL

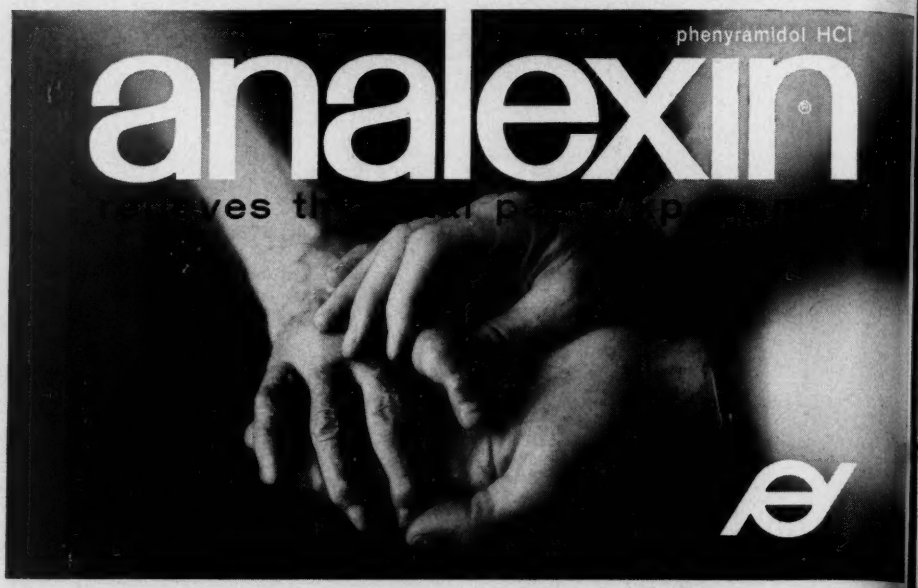
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Analexin's safe therapeutic action has been proven highly effective in relieving pain associated with many conditions seen by the internist. In effectiveness, Analexin's analgesic action is within the range of codeine, yet Analexin is non-narcotic and not narcotic related, and there is no evidence suggestive of tolerance or cumulative effects.[1-8] In fact, Analexin is so safe that dosage may be at hourly intervals if necessary, depending upon the degree of relief required.

If you have been waiting for a safer, more effective analgesic, with a broad range of applications, Analexin could be the answer. Doesn't it deserve a place in your armamentarium?

Analexin®—*for relief of pain*. Each tablet contains 200 mg. phenyramidol HCl.
DOSAGE: Generally, 2 tablets at onset of pain, followed by 1 or 2 tablets at intervals of one to 4 hours as needed.

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DOSAGE: Generally, 2 tablets at onset of pain, followed by 1 or 2 tablets at intervals of one to 4 hours as needed.

Analexin® Syrup—*convenient dosage form for children and adults*. Each 5 cc. contains phenyramidol salicylate 100 mg.
DOSAGE: Children—under 3 yrs., 1 tsp. 3 or 4 times daily; 3-12 yrs., 2 tsp. 3 or 4 times daily. Adults—2 to 4 tsp. every one to 4 hrs.

1. Batterman, R. C.: Ann. New York Acad. Sc. *86*:203, 1960. 2. O'Dell, T. B.: Ann. New York Acad. Sc. *86*:191, 1960. 3. O'Dell, T. B., *et al.*: J. Pharmacol. & Exper. Therap. *128*:65, 1960. 4. O'Dell, T. B., *et al.*: Fed. Proc. *18*:1694, 1959. 5. Gray, A. P., *et al.*: J. Am. Chem. Soc. *81*:4347, 1959. 6. Wainer, A. S.: Ann. New York Acad. Sc. *86*:250, 1960. 7. Clinical data from the files of the Medical Dept., Irwin, Neisler & Co., 1959. 8. Batterman, R. C., *et al.*: Am. J. Med. Sc. *238*:315, 1959.

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Phenylpropanolamine HCl	20 mg.	20 mg.
Phenyltoloxamine citrate	7.5 mg.	7.5 mg.
Chlorpheniramine maleate	2.5 mg.	2.5 mg.

Each teaspoonful (5cc.) of syrup contains the equivalent of one-half tablet.

Outer layer dissolves immediately for prompt effect lasting 3 to 4 hrs.

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Thiamine Mononitrate	10 mg
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'Theragran'® is a Squibb trademark

"nutrition...present as a modifying or complicating factor in nearly every illness or disease state"[1]

1. Youmans, J. B.: Am. J. Med. 25:659 (Nov.) 1958

cardiac diseases "Who can say, for example, whether the patient chronically ill with myocardial failure may not have a poorer myocardium because of a moderate deficiency in the vitamin B-complex? Something is known of the relationship of vitamin C to the intercellular ground substance and repair of tissues. One may speculate upon the effects of a deficiency of this vitamin, short of scurvy, upon the tissues in chronic disease."[2] 2. Kampmeier, R. H.: Am. J. Med. 25:662 (Nov.) 1958.

arthritis "It is our practice to prescribe a multiple vitamin preparation to patients with rheumatoid arthritis simply to insure nutritional adequacy . . ."[3]
3. Fernandez-Herlihy, L: Lahey Clinic Bull. 11:12 (July-Sept.) 1958.

digestive diseases Symptoms attributable to B-vitamin deficiency are commonly observed in patients on peptic ulcer diets.[4] Daily administration of therapeutic vitamins to patients with hepatitis and cirrhosis is recommended by the National Research Council.[5] 4. Sebrell, W. H.: Am. J. Med. 25:673 (Nov.) 1958. 5. Pollack, H., and Halpern, S. L.: Therapeutic Nutrition, National Academy of Sciences and National Research Council, Washington, D. C., 1952, p. 57.

degenerative diseases "Studies by Wexberg, Jolliffe and others have indicated that many of the symptoms attributed in the past to senility or to cerebral arteriosclerosis seem to respond with remarkable speed to the administration of vitamins, particularly niacin and ascorbic acid. These facts indicate that the vitamin reserve of aging persons is lowered, even to the danger point, more than is the case in the average American adult."[6] 6. Overholser, W., and Fong, T. C. C. in Stieglitz, E. J.: Geriatric Medicine, 3rd edition, J. B. Lippincott, Philadelphia, 1954, p. 264.

infectious diseases Infections cause a lowering of ascorbic acid levels in the plasma; and the absorption of this vitamin is reduced in diarrheal states.[7] 7. Goldsmith, G. A.: Conference on Vitamin C. The New York Academy of Sciences, New York City, Oct. 7 and 8, 1960. Reported in: Medical Science 8:772 (Dec.10) 1960.

diabetes Diabetics, like all patients on restricted diets, require an extra source of vitamins.[8] "Rigidly limiting the bread intake of the diabetic patient automatically eliminates a large amount of thiamin from the diet. . . . There is some evidence of interference with normal riboflavin utilization during catabolic episodes."[9]
8. Duncan G. G.: Diseases of Metabolism 4th edition W. B. Saunders, Philadelphia, 1959, p. 812. 9. Pollack, H.: Am. J. Med. 25:708 (Nov.) 1958.

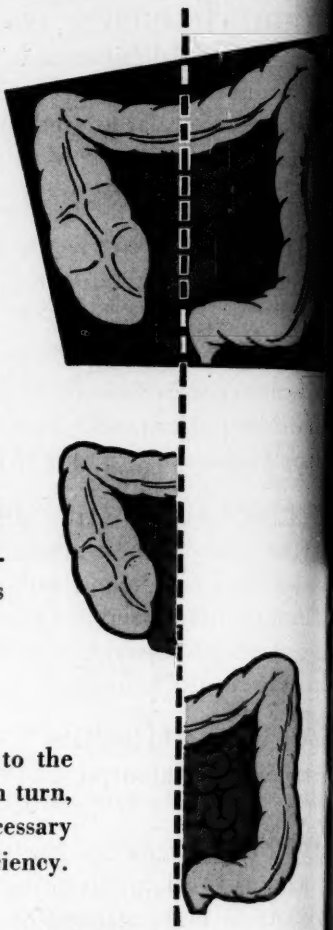
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MODANE provides Danthron—non-irritating, non-habit-forming, overnight de-constipant which acts gently, positively, on the large bowel only.

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MODANE supplies Pantothenic Acid vital to the body's formation of coenzyme A which is, in turn, essential for acetylation of choline—so necessary for normal bowel tone and peristaltic efficiency.

3 IDEAL DOSAGE FORMS

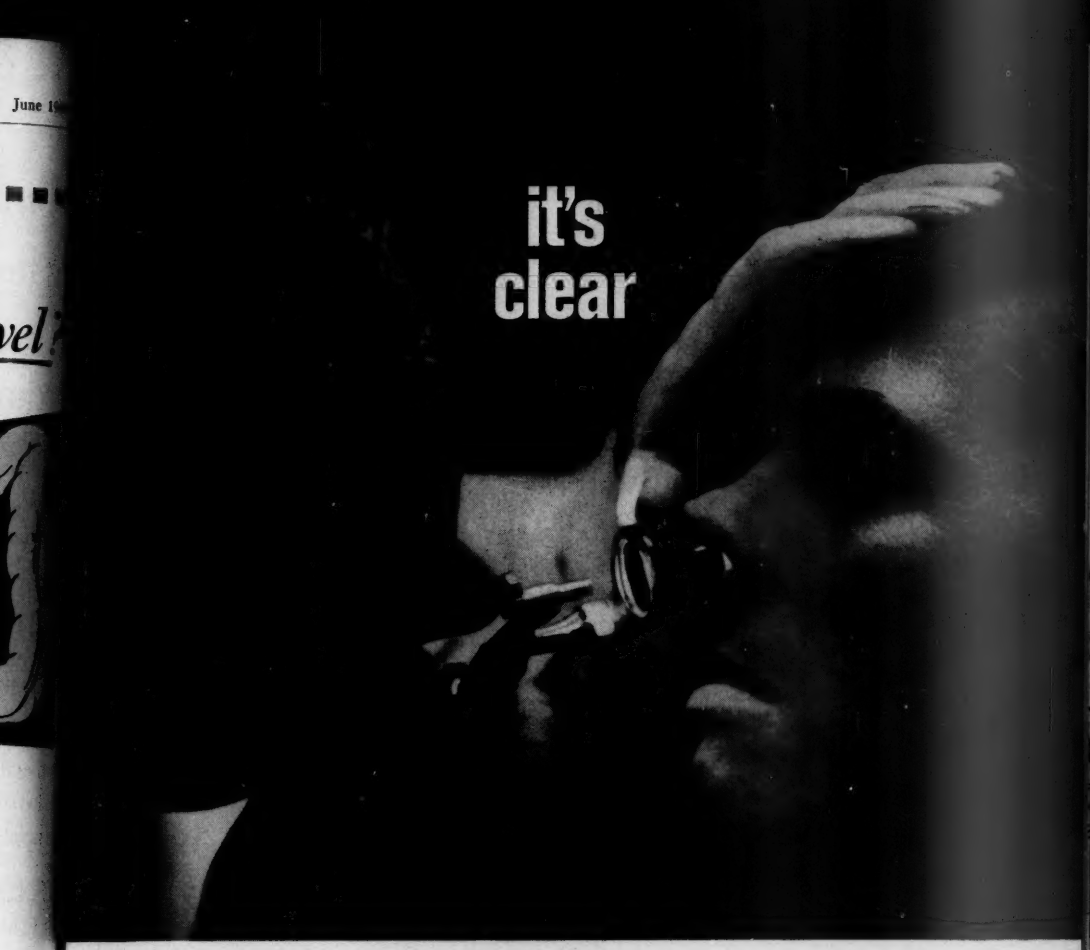
Each Modane Tablet contains 75 mg. Danthron (1.8 Dihydroxyanthraquinone) and 25 mg. Calcium Pantothenate. Each Modane Mild Tablet and each teaspoonful Modane Liquid contains 37.5 mg. Danthron and 12.5 mg. Calcium Pantothenate. Dosage — 1 tablet, teaspoonful, or fractional teaspoonful, immediately after the evening meal.

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DIMETAPP Extentabs contain Dimetane® (parabromdylamine [brompheniramine] maleate 12 mg., phenylephrine HCl 15 mg., and phenylpropanolamine HCl 15 mg. Dependable Extentab construction assures relief of symptoms for up to 12 hours with 1 tablet.

Dosage: Adults — 1 Extentab q. 8-12 hours. Children over 6 — 1 Extentab q. 12 hours. **Precautions:** In high dosage some drowsiness may infrequently occur from Dimetane. As with all preparations containing sympathomimetic amines, DIMETAPP should be administered with caution to patients with cardiac or peripheral vascular diseases or hyperthyroidism. **Contraindication:** Patients sensitive to antihistamines. **Supplied:** Bottles of 100 and 500.

*New England J. Med. 261:478, 1959
(Schiller, I. W. and Lowell, F. C.)

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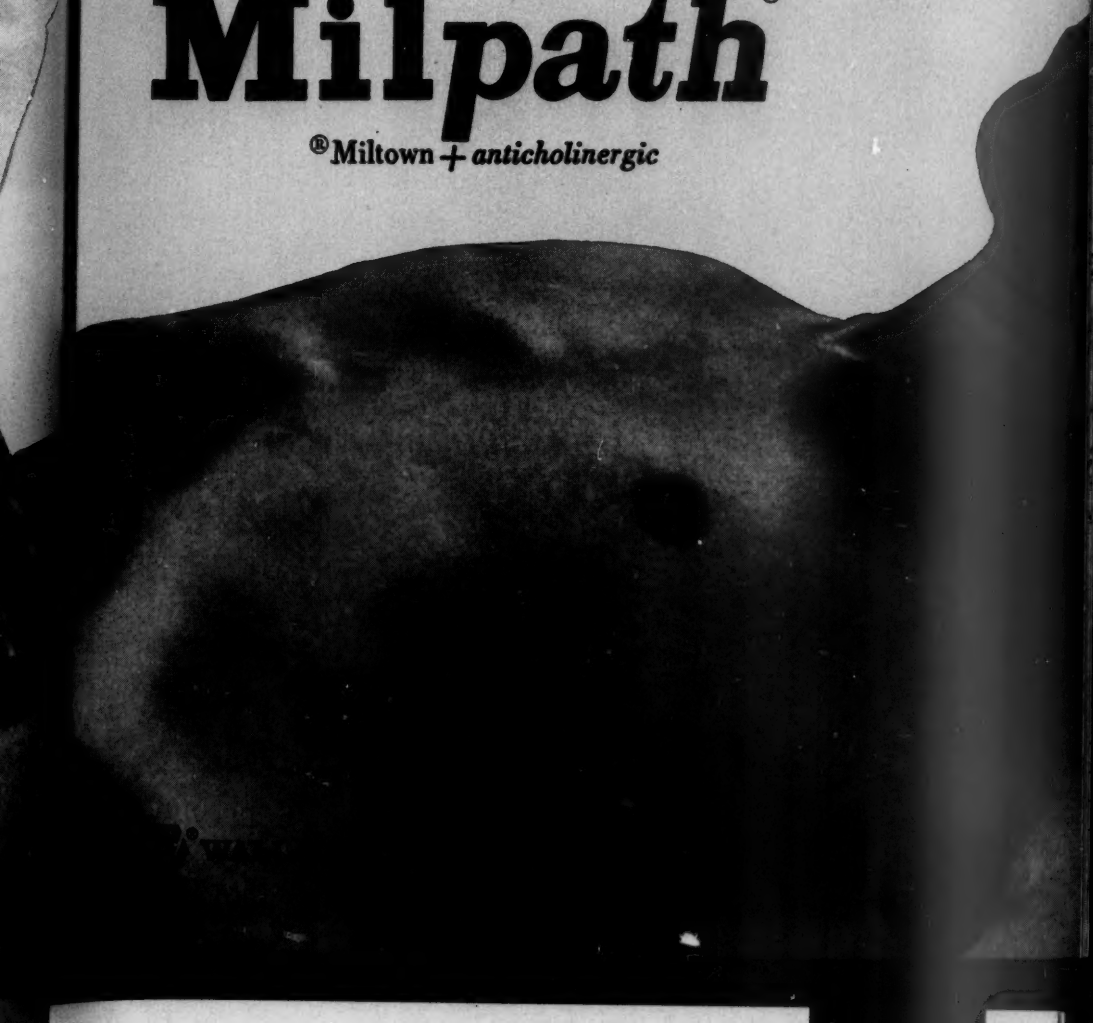
IN GASTROINTESTINAL DYSFUNCTION

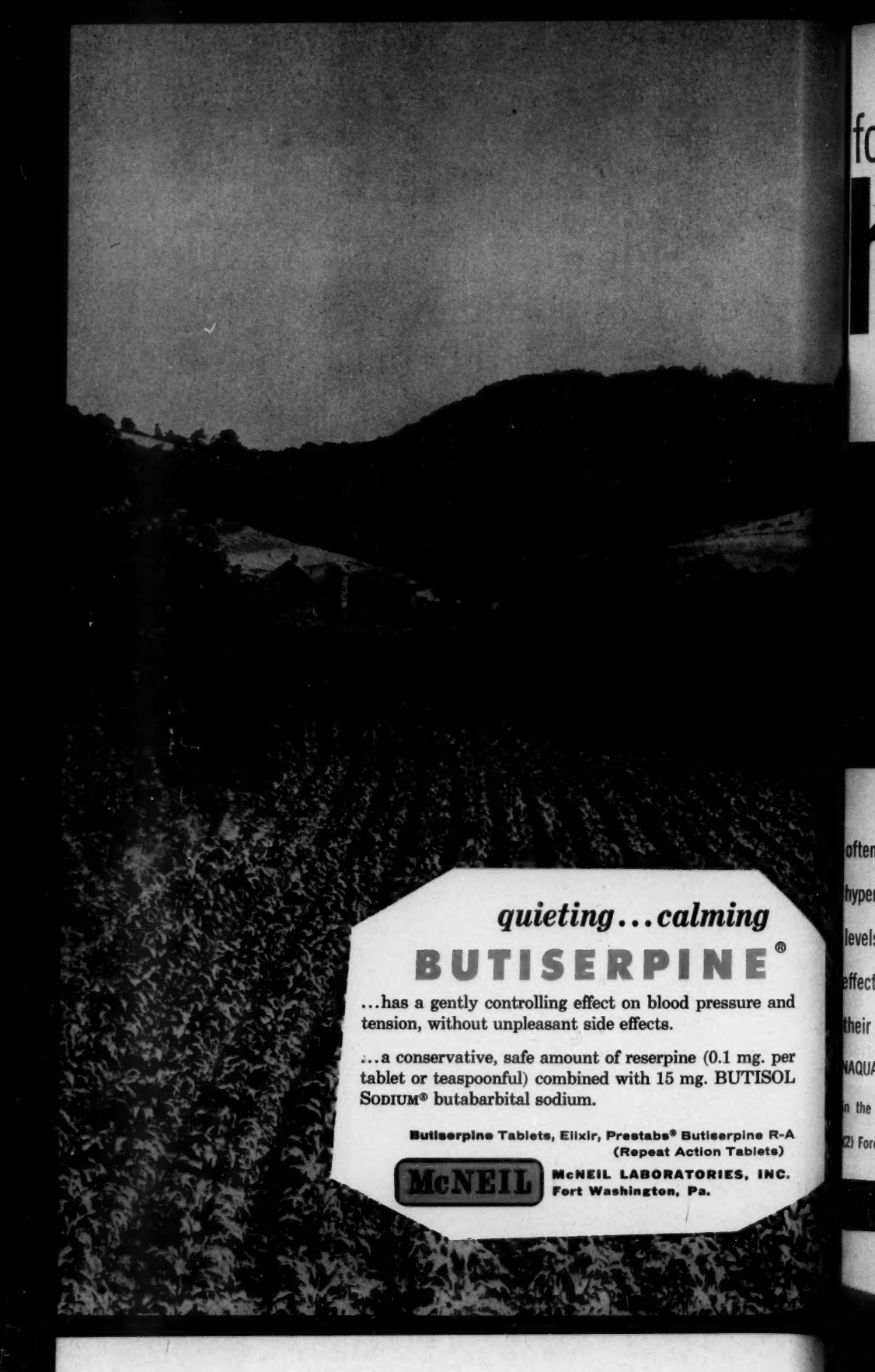
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often the only drug required for satisfactory reduction of blood pressure in both mild and moderate hypertension...commonly relieves headache, palpitation, etc.[1]...may further reduce blood pressure levels reached on previous regimens[2]...usually obviates need for potassium supplements...potentiates effect of some adjunctive antihypertensive agents, decreasing their dosage needs, thereby reducing their potential side effects...economically priced for special benefit of long-term patients. **Packaging:** NAQUA Tablets, 2 and 4 mg., scored, bottles of 100 and 1000. **References:** (1) Cohen, B. M.: Newer Saluretic Agents in the Therapy of Hypertension, paper presented at 6th Internat. Cong. Int. Med., Basel, Switzerland, Aug. 24-27, 1960. (2) Ford, R. V.: Am. J. Cardiol. 5:407, 1960.

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A 5-year study[1] of long-term anticoagulation with COUMADIN (warfarin sodium) in office practice patients has demonstrated that such treatment reduces the probability of further infarctions in the postinfarct patient and is effective in preventing a first infarction in patients with angina.

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"The most significant advantage is the great ease in maintaining patients in a therapeutic range. It has been rewarding to find, month after month, patients varying no more than three or four seconds in their prothrombin times on their established dosage of Warfarin sodium [COUMADIN]."[1]

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coagulant[3,4] and as "the best anticoagulant avail
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Full range of oral and parenteral dosage forms—Coumadin® (warfarin sodium) is available as: Scored tablets—2 mg., lavender; 5 mg., peach; 7½ mg., yellow; 10 mg., white; 25 mg., red. Single Injection Units—one vial, 50 mg., and one 2 cc. ampul Water for Injection; one vial, 75 mg., and one 3 cc. ampul Water for Injection.

Average Dose: Initial, 40-60 mg. for elderly and/or
tated patients, 20-30 mg. Maintenance, 5-10 mg. da
as indicated by prothrombin time determinations.

1. Nora, J. J.: M. Times, May, 1961. 2. Nora, J. J.: J.A.M.A. 174:115,
1960. 3. Moser, G., et al.: J.A.M.A. 167:799, June 7, 1958. 4. Moser, R.
ease-a-Month, Chicago, Yr. Bk. Pub., Dec., 1960, p. 12. 5. Meyer,
Postgrad. Med. 24:110, Aug., 1958.

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in any emetic situation

Tigan is safe and sound

Against nausea there's nothing more effective or, for that matter, quite so safe as Tigan. Tigan has **one** demonstrable pharmacologic property: it blocks emetic impulses, primarily by direct action at the chemoreceptor trigger zone (CTZ) of the medulla.[1] Tigan thus **stops** active vomiting as effectively as it prevents nausea and emesis.[2-5] Tigan is not a converted antihistamine, tranquilizer or sedative; it may be used even where older antiemetics are contraindicated.

USUAL DOSAGE

ADULTS: Capsules — The usual dosage is 100 mg to 200 mg, three or four times daily. In nausea and vomiting of pregnancy, one 250 mg capsule at bedtime and one immediately upon awakening. In severe cases this dose may be repeated up to a total of three or four capsules daily.

Intramuscular Injection — 200 mg (2 cc), one to four times daily.

Suppositories — 200 mg (one suppository), three or four times daily.

CHILDREN: Capsules — For children 30 to 90 pounds, one 100 mg capsule, three or four times daily.

Intramuscular Injection — Under 30 pounds, 50 mg (½ cc); 30 to 60 pounds, 100 mg (1 cc); 60 to 90 pounds, 150 mg (1½ cc) — one to four times daily.

Suppositories — Under 30 pounds, 100 mg (½ suppository); 30 to 90 pounds, 100 mg to 200 mg (½ to 1 suppository) — three to four times daily.

Note: There are no known contraindications or special precautions to be taken with Tigan therapy. Because Tigan has no sedative or tranquilizer properties, it is **not** necessary for patients to refrain from operating an automobile or other mechanical equipment while on Tigan medication.

Packages: Capsules, 100 mg, blue and white — bottles of 100 and 500; 250 mg, blue — bottles of 50. Ampuls, 2 cc (100 mg/cc) — boxes of 6 and 25. Multidose vials, 20 cc (100 mg/cc) — boxes of 1. Suppositories, 200 mg — boxes of 6.

References: 1. W. Sunshine, G. A. Iwamoto, J. F. Keith and R. J. Blagden: **J. Pharmacol. & Exper. Therap.** 126: 1959. 2. D. C. Brandman: paper read at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. 3. I. Rosoff, W. B. Abrams, J. Kaufman, L. Goldman and A. Bernstein: **J. Mt. Sinai Hosp.** 9: 1958. 4. W. B. Abrams, I. Rosoff, J. Kaufman, L. M. Goldman and A. Bernstein: **New York J. Med.**, 59: 1959. 5. D. C. Brandman: **Gastroenterology**, 38: 1960.

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Protects the angina patient better than vasodilators alone

Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, can delay recovery.

This is why Miltrate gives better protection for the heart than vasodilators alone in coronary insufficiency, angina pectoris and postmyocardial infarction.

Miltrate contains PETN (pentaerythritol tetranitrate), acknowledged as basic therapy for long-acting vasodilation. . . .

What is more important—Miltrate provides Miltown, a tranquilizer which, unlike phenobarbital, relieves tension in the apprehensive angina patient without inducing daytime fogginess.

Thus, your patient's cardiac reserve is protected against his fear and concern about his condition; his operative arteries are dilated to enhance myocardial blood supply—and he can carry on normal activities more effectively since his mental acuity is unimpaired by barbiturates.

REFERENCES: 1. Ellis, L. B. *et al.:* Circulation *17*:945, May 1958. 2. Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. 3. Riseman, J.E.F.: New England J. Med. *261*:1017, Nov. 12, 1959. 4. Russek, H. I. *et al.:* Circulation *12*:169, Aug. 1955. 5. Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. 6. Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. 7. Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

Supplied: Bottles of 50 tablets. Each tablet contains 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.

Dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime, according to individual requirements. CML-3619

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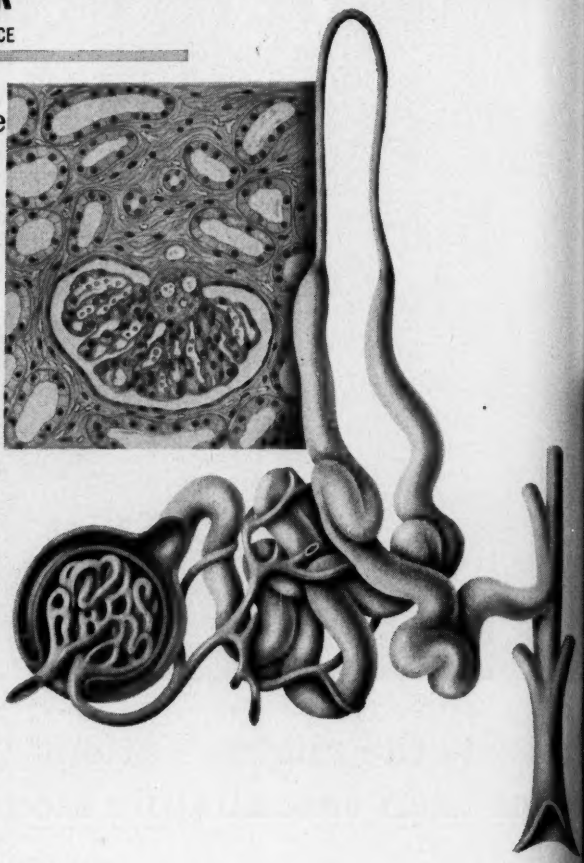
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CLINICAL BRIEFS FOR MODERN PRACTICE

will today's vigilance help avoid tomorrow's diabetic complication?



How long and happily your diabetic patient lives depends largely on how well he avoids or delays renal and cardiac vascular degeneration. One of the best safeguards against secondary diabetic manifestations is the close surveillance of glucosuria *and proteinuria.* Because the continuity of control is vital in this regard, routine tests for glucosuria and proteinuria are of more than daily significance. The development of proteinuria may be directly related to the degree of diabetic control, and possibly provide an early forewarning of the onset of diabetic nephropathy.* Thus, routine testing for both not only helps avoid current accident, but also forewarns against the cumulative manifestations of diabetes.

An extremely practical measure of both protein and glucose in the urine is provided by URISTIX.® This new "dip-and-read" reagent strip gives *two* accurate readings within *ten* seconds after a *single* dip. URISTIX is clean and easy to use, either for office diagnosis or control of home therapy. It eliminates delay, guesswork, and fussing with equipment, and it is completely disposable. A standardized color chart is on the URISTIX bottle label for convenience.

URISTIX is also an excellent combination for routine testing of pregnant patients.

*Nagy El Mahallawy, M., and Sabour, M. S.: J.A.M.A. *173*:1783 (Aug. 20) 1960.

colorimetric "dip-and-read" test for both proteinuria and glucosuria

URISTIX®
BRAND Reagent Strips

1 DIP . . . 10 SECONDS . . . 2 RESULTS
available: URISTIX Reagent Strips, bottles of 125.

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AMES
COMPANY, INC
Elkhart • Indiana
Toronto • Canada

DORNWAL®

has been called "The general tranquilizer for general practice."

Suppose the physician visiting this patient finds that he has to be hospitalized. Certainly he wants an alert but not excited fellow who can respond to the history and physical on admission. Depending on the condition, of course, the thing to do is to give the patient one or two tablets of Dornwal before he ever leaves his home.

Dornwal will calm the patient but won't make him drowsy or give him feelings of depersonalization. And what's more, while Dornwal most assuredly tranquilizes, it won't interfere with most other medications that your subsequent examination or laboratory studies may indicate.

Since every man in general practice encounters such situations almost daily, it makes good sense to keep some tablets in one's bag, doesn't it? We will be glad to send you a supply.

Dosage: One or two 200 mg. tablets three times a day. Children, age 6 to 16, one or two 100 mg. tablets two times a day.

Supplied: 200 mg. yellow scored tablets, and 100 mg. pink tablets, each in bottles of 100 and 500.

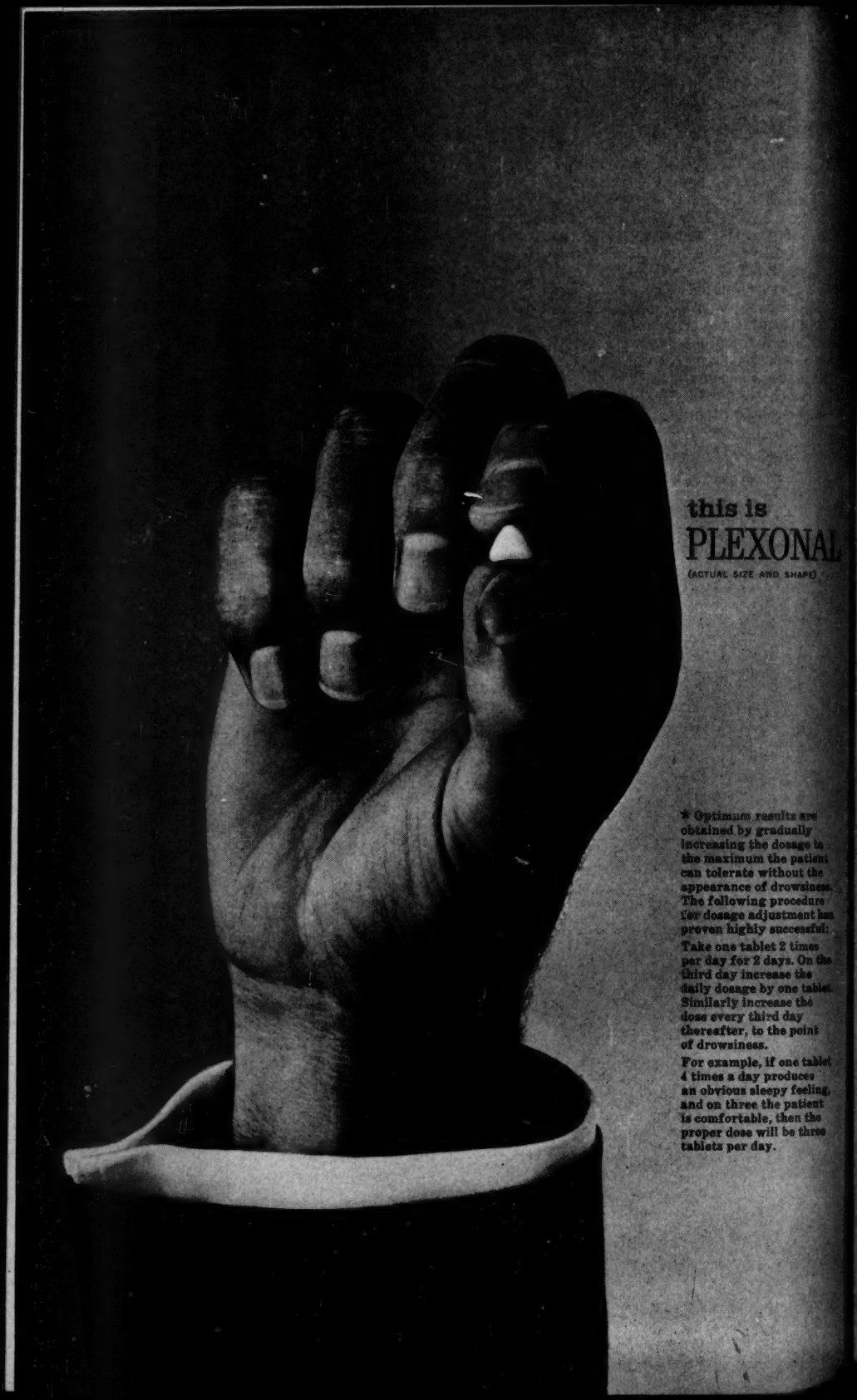
P.S. For the "Genericist," Dornwal is amphenidone.

No absolute contraindications to the use of Dornwal are known. There have been no reports or evidence of habituation, addiction or drug tolerance in animal or clinical studies. Dornwal is relatively free from untoward effects when administered at recommended dosages.

Maltbie Laboratories Division,
Wallace & Tiernan Inc., Belleville 9, N. J.

Maltbie





* Optimum results are obtained by gradually increasing the dosage to the maximum the patient can tolerate without the appearance of drowsiness. The following procedure for dosage adjustment has proven highly successful:

Take one tablet 2 times per day for 2 days. On the third day increase the daily dosage by one tablet. Similarly increase the dose every third day thereafter, to the point of drowsiness.

For example, if one tablet 4 times a day produces an obvious sleepy feeling, and on three the patient is comfortable, then the proper dose will be three tablets per day.

superior daytime relaxing agent

(NOT A TRANQUILIZER)

PLEXONAL®



Comparative clinical studies show that PLEXONAL is superior to meprobamate or barbiturates for daytime relaxation[1,2]

"Plexonal was preferred (superior therapeutic effect) by 73.7 per cent of the patients, whereas 11.1 per cent preferred meprobamate, a ratio of 6.6 to 1. . . . 30.5 per cent noted adverse reactions to meprobamate as compared to 7 per cent in respect to Plexonal. . . . Plexonal gave better results than did any of the sedative or relaxing agents that have been available during our experience covering the previous 15 years."[1]

In 26 older age cardiac patients, "A comparison of Plexonal with the therapy previously employed showed that 17 did better on Plexonal than on meprobamate, 6 did better on meprobamate than on Plexonal and 3 responded the same to both."[2]

Indications: Anxiety, tension, apprehension, nervousness, irritability, restlessness, hyperexcitability.

Extremely well tolerated by geriatric patients who need mild sedation, as well as by depressed patients.

Dosage: One tablet 3 or 4 times a day is adequate for most patients. However, some require up to six tablets per day, whereas others respond adequately to as little as 1 tablet per day.*

Composition: Each tablet contains sodium diethylbarbiturate 45 mg., sodium phenylethylbarbiturate 15 mg., sodium isobutylallylbarbiturate 25 mg., scopolamine hydrobromide 0.08 mg., dihydroergotamine methanesulfonate 0.16 mg.

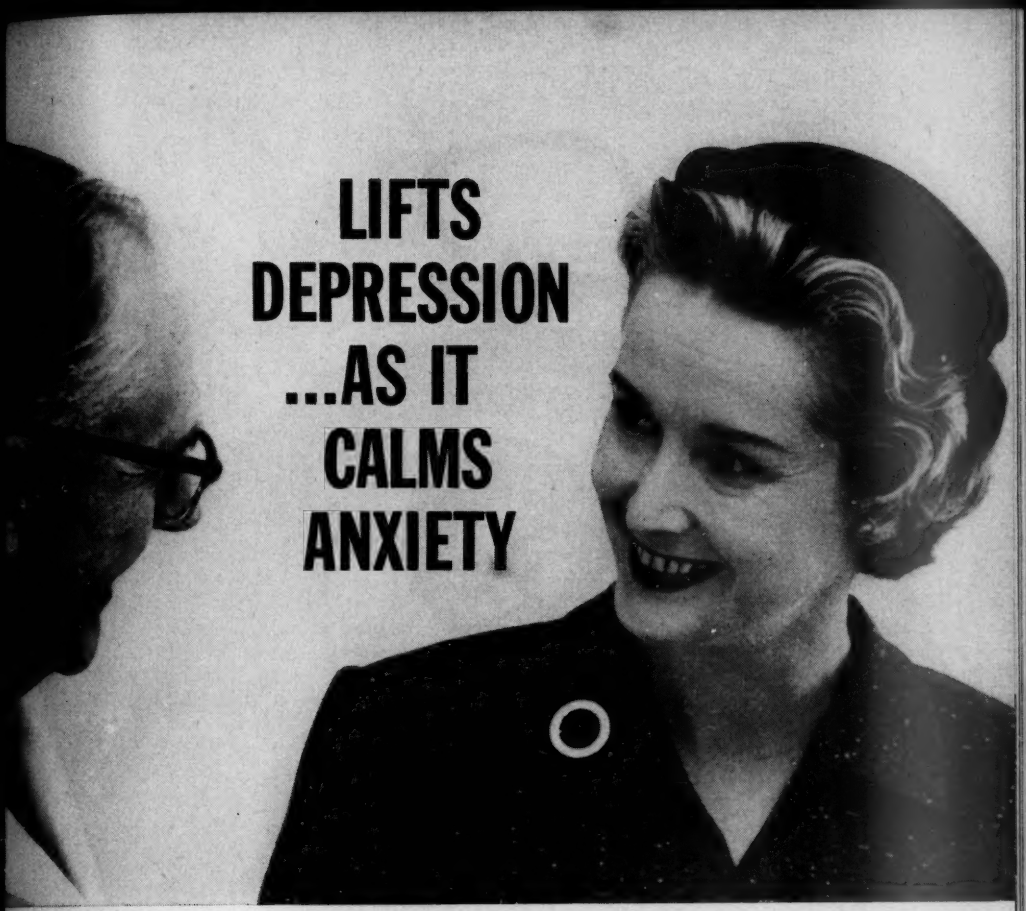
1. Scheifley, C. H.: Proc. Staff Meet. Mayo Clin. 34:408 (Aug. 19) 1959.
2. Davanloo, H.: Am. J. of Psychiat. 117:740 (Feb.) 1961.

ORIGINAL RESEARCH SERVING THE PHYSICIAN

SANDOZ



When the rhythm is wrong...PRONESTYL® HYDROCHLORIDE



"I feel like my old self again!" Thanks to your balanced Deprol therapy, normal drive and interest have replaced her emotional fatigue.

Brightens up the mood, brings down tension

Balanced action – avoids "seesaw" effects of energizers and amphetamines.

Acts rapidly – you see improvement in a few days.

Acts safely – no danger of liver or blood damage.

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.
Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.
Supplied: Bottles of 50 light-pink, scored tablets.

WALLACE LABORATORIES / *Cranbury, N. J.*

CD-4708

▲Deprol▲®

Mail this coupon for clinical supply of Deprol

Dept. D-12
Professional Services Dept.
Wallace Laboratories
Cranbury, N. J.

Gentlemen: *Please send me a clinical supply of Deprol for the treatment of depression.*

Dr. .....

Street .....

City ..... Zone ..... State .....

Type of practice .....



Iron utilization improves her picture

Iron utilization depends principally upon the rate of erythropoiesis[1,2] which, in turn, is controlled by the hormone, erythropoietin.[3,4] Cobalt is the only clinically proved agent which enhances the formation of erythropoietin[5,6] ...providing a rational physiologic approach to the treatment of anemia. □ RONCOVITE-MF, through cobalt-created erythropoietin, produces a more rapid and complete red blood cell and hemoglobin response in iron deficiency anemia of pregnancy.[7-9] Typically, in a study of pregnant patients, "... utilization of orally administered iron was increased roughly twofold by the simultaneous administration of cobalt."[7]

Each tablet contains: cobalt chloride (cobalt as Co, 3.7 mg.) 15 mg. and ferrous sulfate, exsiccated, 100 mg.

RONCOVITE®-mf

(1) Bothwell, T. H.; Pirzio-Biroli, G., and Finch, C. A.: J. Lab. & Clin. Med. 51:24, 1958. (2) Beutler, E., and Buttenwieser, E.: J. Lab. & Clin. Med. 53:274, 1960. (3) Gordon, A. S.: Physiol. Rev. 39:1, 1959. (4) Rosse, W. F., and Garney, C. W.: J. Lab. & Clin. Med. 53:446, 1959. (5) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L. F.: Blood 13:55, 1958. (6) Murdock, H. R., Jr.: J. Am. Pharm. A. (Scient. Ed.) 48:140, 1959. (7) Center, W. M.: Clin. Med. 7:713, 1960. (8) Craig, P. E.: Clin. Med. 6:597, 1959. (9) Holly, R. G.: Clin. Obst. & Gynec. 1:15, 1958.

LLOYD BROTHERS, INC.
Cincinnati 29, Ohio

ANNOUNCING
A NEW FORMULATION
FOR PATIENTS WITH GASTRITIS
AND CERTAIN OTHER
GASTROINTESTINAL PROBLEMS
often *succeeds*
where other therapeutic modes fail



Controls pain and discomfort of gastritis and related disorders

. . . direct anesthetic action

For patients with tendency towards constipation

New OXAINE M, with topical anesthetic oxethazaine, stops pain of gastritis directly by prolonged desensitization of the irritated gastric mucosa.



Anesthetic, demulcent and antacid actions, encourage healing, relieve pain, bloating, belching, queasiness and nausea. OXAINE M contains magnesium hydroxide in the alumina gel vehicle to increase palatability and decrease constipation —elicits patient cooperation and permits long-term use when necessary. For patients with esophagitis, OXAINE, without magnesium hydroxide, is available.

Although not a "caine," oxethazaine is approximately 500 times as potent topically as cocaine. Its duration of action and effectiveness remain almost unaltered despite variation in pH or ebb and flow of gastric contents. Alumina gel forms a diffuse coating over mucosa and further prolongs the action of oxethazaine.

Wyeth ®
SERVICE TO MEDICINE

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CLINICAL STUDIES CONFIRM EFFICACY, WIDE MARGIN OF SAFETY

Gastritis Symptoms Readily and Reliably Relieved

Complete relief of substernal or upper abdominal pain in 88 of 92 previously refractory patients with chronic gastritis[1] was obtained on *oxethazaine in alumina gel,* dietary controls, occasional gastric suction and rest. As therapy continued, dietary restrictions could be relaxed. No significant side effects developed even after 18 months' use.

In another study[2] of 56 patients with gastrointestinal disturbances—including 18 gastritis cases—53 patients displayed complete or partial relief when *oxethazaine in alumina gel* (*or alumina gel plus magnesium hydroxide*) was added to the therapeutic regimen.

Excellent Response Demonstrated in Other Gastrointestinal Disturbances

Oxethazaine in alumina gel is of value in a variety of other gastrointestinal conditions, including:

peptic ulcer[2,3] . . . relieves pain and promotes healing of duodenal and gastric ulcers

esophagitis[4] . . . . relieves postprandial heartburn and acid regurgitation in chronic esophagitis without stricture

irritable bowel[5] . . . relieves discomfort and exaggerated gastrocolic reflex in the irritable bowel syndrome

References: 1. Deutsch, E., and Christian, H.J.: J. Am. Med. Assoc. *169*:2012 (April 25) 1959.
2. Moffitt, R.E.: Rhode Island Med. J. *44*:151 (March) 1961.
3. Hollander, E.: Am. J. Gastroenterol. *34*:613 (Dec.) 1960.
4. Jankelson, I.R., and Jankelson, O.M.: Am. J. Gastroenterol. *32*:636 (Nov.) 1959.
5. Jankelson, I.R., and Jankelson, O.M.: Am. J. Gastroenterol. *32*:719 (Dec.) 1959.

For further information on limitations, administration and prescribing of OXAINE M *and* OXAINE, *see descriptive literature or current Direction Circular.*

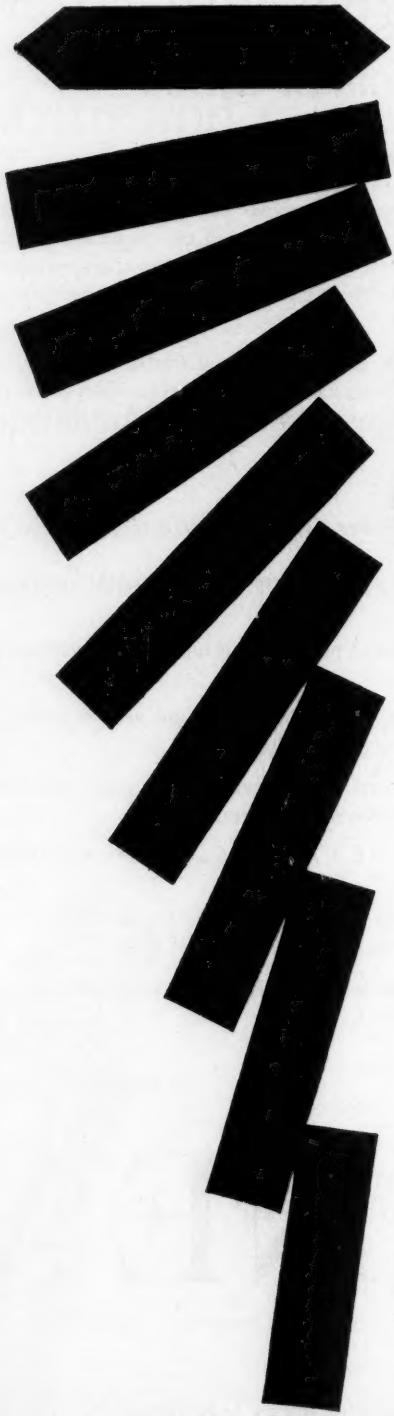
NEW *a palatable suspension*

OXAINE® M

Oxethazaine in Alumina Gel with Magnesium Hydroxide, Wyeth

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outlasting all trends in analgesia



CODEINE

There are modes in medication, just as in all the things of man. Medications for pain have come and gone, while codeine, a classic analgesic and antitussive, has become an axiom in medical practice.

Versatile codeine is effective orally or parenterally, alone or in combination. In therapeutic dosage codeine rarely produces dependence; judiciously given, it never disappoints. And it is well tolerated.

Reasons enough for a drug to outlast all trends in analgesia.

Mallinckrodt®

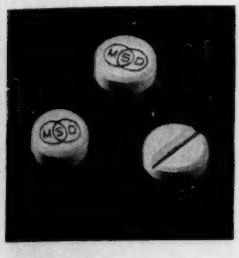
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in edema or hypertension

more doctors are prescribing—

more patients are receiving the benefits of—

more clinical evidence exists for—



DIURIL®

CHLOROTHIAZIDE

than for any other diuretic-antihypertensive

DIURIL is unique. There is no other brand of chlorothiazide.

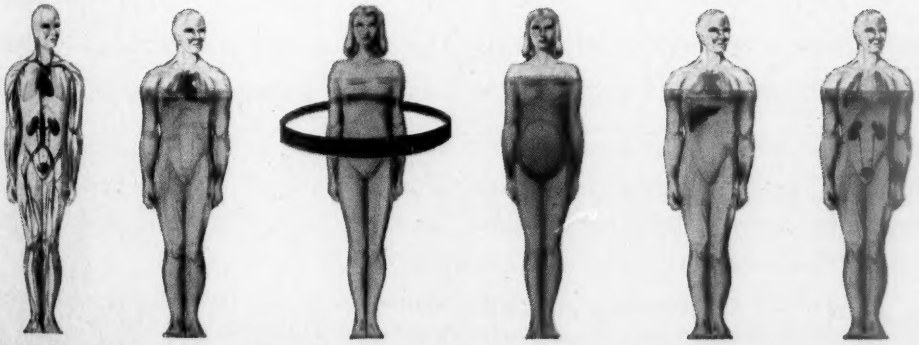
Dosage: Edema—One or two 500-mg. tablets DIURIL once or twice a day. Hypertension—One 250-mg. tablet DIURIL or one 500-mg. tablet DIURIL two to three times a day.

Supplied: 250-mg. and 500-mg. scored tablets DIURIL chlorothiazide in bottles of 100 and 1000.

DIURIL is a trademark of Merck & Co., INC.

Additional information is available to the physician on request.

MSD MERCK SHARP & DOHME
Division of Merck & Co., INC., West Point, Pa.



HYPERTENSION **CONGESTIVE FAILURE** PREMENSTRUAL TENSION **EDEMA OF PREGNANCY** CIRRHOSIS WITH ASCITES **RENAL EDEMA**

'MYSOLINE'® IN EPILEPSY

BRAND OF PRIMIDONE



CLEAR EXPRESSION OF CONTROL

"The most important drug to be introduced in recent years... This is the drug of choice in the treatment of psychomotor epilepsy and in focal seizures, and is of particular value in the handling of intractable cases of grand mal epilepsy."*

Employed alone or in combination, "Mysoline" exhibits dramatic effectiveness, often where epilepsy has remained intractable to maximal doses of other anticonvulsants. Virtual freedom from toxic reactions is assured by a wide safety margin.

*Forster, F. M.: Wisconsin M. J. 58:375 (July) 1959. Literature and bibliography on request.

AYERST LABORATORIES NEW YORK 16, N. Y. • MONTREAL, CANADA

"Mysoline" is available in the United States by arrangement with Imperial Chemical Industries, Ltd.

THERAPEUTIC INDEX

'MYSOLINE'®

BRAND OF PRIMIDONE

IN EPILEPSY

Indications: In the control of grand mal and psychomotor seizures.

Usual Dosage: *Patients receiving no other anticonvulsants—Children under 8 years:* Order of dosage same as for adults, but start with ½ tablet (0.125 Gm.) daily and increase by ½ tablet daily each week, until control. (Where a smaller starting dose is required, use 50 mg. tablet.)

Adults and Children (over 8 years): 1 tablet (0.25 Gm.) daily (preferably at bedtime) for 1 week. Increase by 1 tablet daily each week, until control. Dosage exceeding 2 Gm. daily presently not recommended.

Patients already receiving other anticonvulsants—Children under 8 years: Initially one-half the adult dose, or 0.125 Gm. daily. Gradual increases and decreases as described in adult regimen. (Where a smaller starting dose is required, use 50 mg. tablet.)

Adults and Children (over 8 years): 0.25 Gm. daily, and gradually increased while the dosage of the other drug(s) is gradually decreased. Continued until satisfactory dosage level is achieved for combination, or until other medication is completely withdrawn.

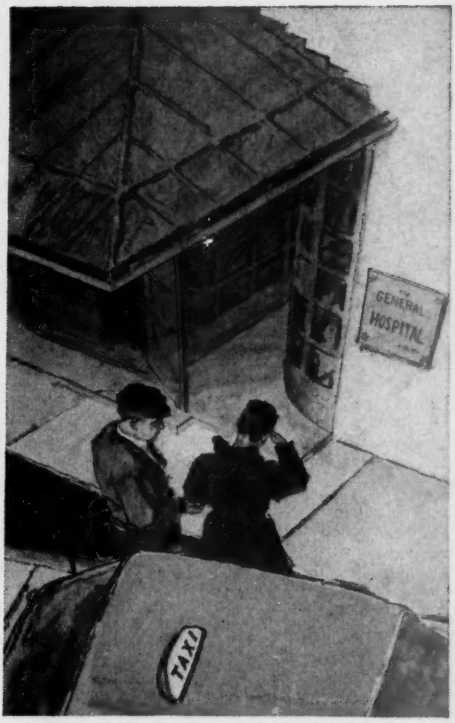
When therapy with "Mysoline" alone is the objective, the transition should not be completed in less than two weeks.

Precautions: Side reactions, when they occur, are usually mild and transient, tending to disappear as therapy is continued or as dosage is adjusted. Commonly reported side effects are drowsiness, ataxia, vertigo, anorexia, irritability, general malaise, nausea and vomiting. No serious irreversible toxic reactions have been observed. (Occasionally, megaloblastic anemia has been reported in patients on "Mysoline." The condition is readily reversible by folic acid therapy, 15 mg. daily, while "Mysoline" is continued.) As with any drug used over prolonged periods of time, it is recommended that routine laboratory studies be made at regular intervals.

Supplied: No. 3430—"Mysoline" Tablets—Each scored tablet contains 0.25 Gm. (250 mg.) of Primidone, in bottles of 100 and 1,000. No. 3431—"Mysoline" Tablets—Each scored tablet contains 50 mg. of Primidone, in bottles of 100 and 500.

Also available: No. 3850—"Mysoline" Suspension—Each 5 cc. (teaspoonful) contains 0.25 Gm. of Primidone, in bottles of 8 fluidounces.

6116



DORNWAL® IS THE RIGHT TRANQUILIZER TO USE IN MOST CASES

Take this patient going to the hospital for surgery or diagnostic biopsy. Dornwal, given a few hours before admission or just afterwards, gently allays her anxiety to just the right healthy degree.

But why Dornwal? The answer's important to you. For one thing, every physician wants his patient to be tranquil or in good spirits, if that is possible, upon entering the hospital.

And if you want a tranquil and yet responsive patient — one who can answer questions clearly — then Dornwal's your tranquilizer, because Dornwal is only a tranquilizer and not a sedative.

Dornwal does only what it is supposed to do — tranquilize — and that singleness of effect is very important both to you and to most people facing surgery or diagnostic examinations of any sort. We suggest one or two tablets 3 times a day.

Dosage: One or two 200 mg. tablets three times a day. Children, age 6 to 16, one or two 100 mg. tablets two times a day.

Supplied: 200 mg. yellow scored tablets, and 100 mg. pink tablets, each in bottles of 100 and 500.

P.S. For the "Genericist," Dornwal is amphenidone

No absolute contraindications to the use of Dornwal are known. There have been no reports or evidence of habituation, addiction or drug tolerance in animal or clinical studies. Dornwal is relatively free from untoward effects when administered at recommended dosages.

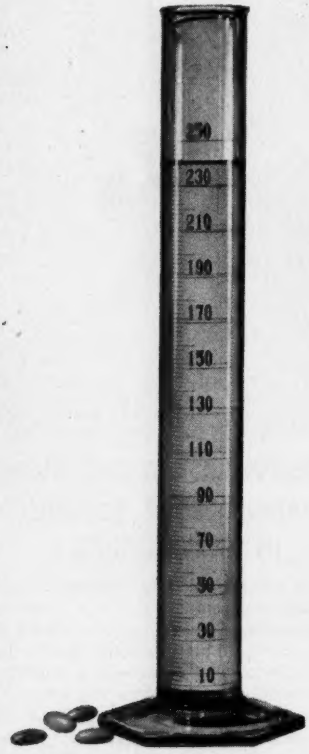
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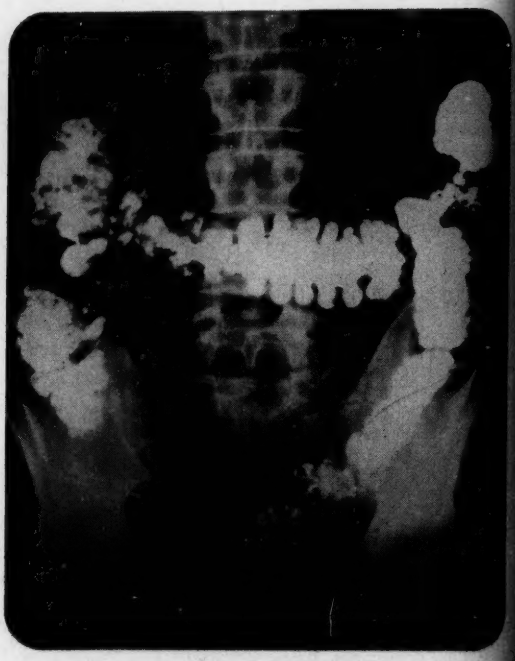
Maltbie

PDW-13

In acute and chronic diarrhea the most effective symptomatic solution to the dual problem:

dual action **Sorboquel®** (polycarbophil-thihexinol methylbromide) *tablets*





fast action **1**
for too fluid feces:
Exceptional water-binding capacity of polycarbophil to absorb free fecal water

fast action **2**
for too frequent evacuations:
Superior, yet selective, nonopiate antimotility action of thihexinol methylbromide

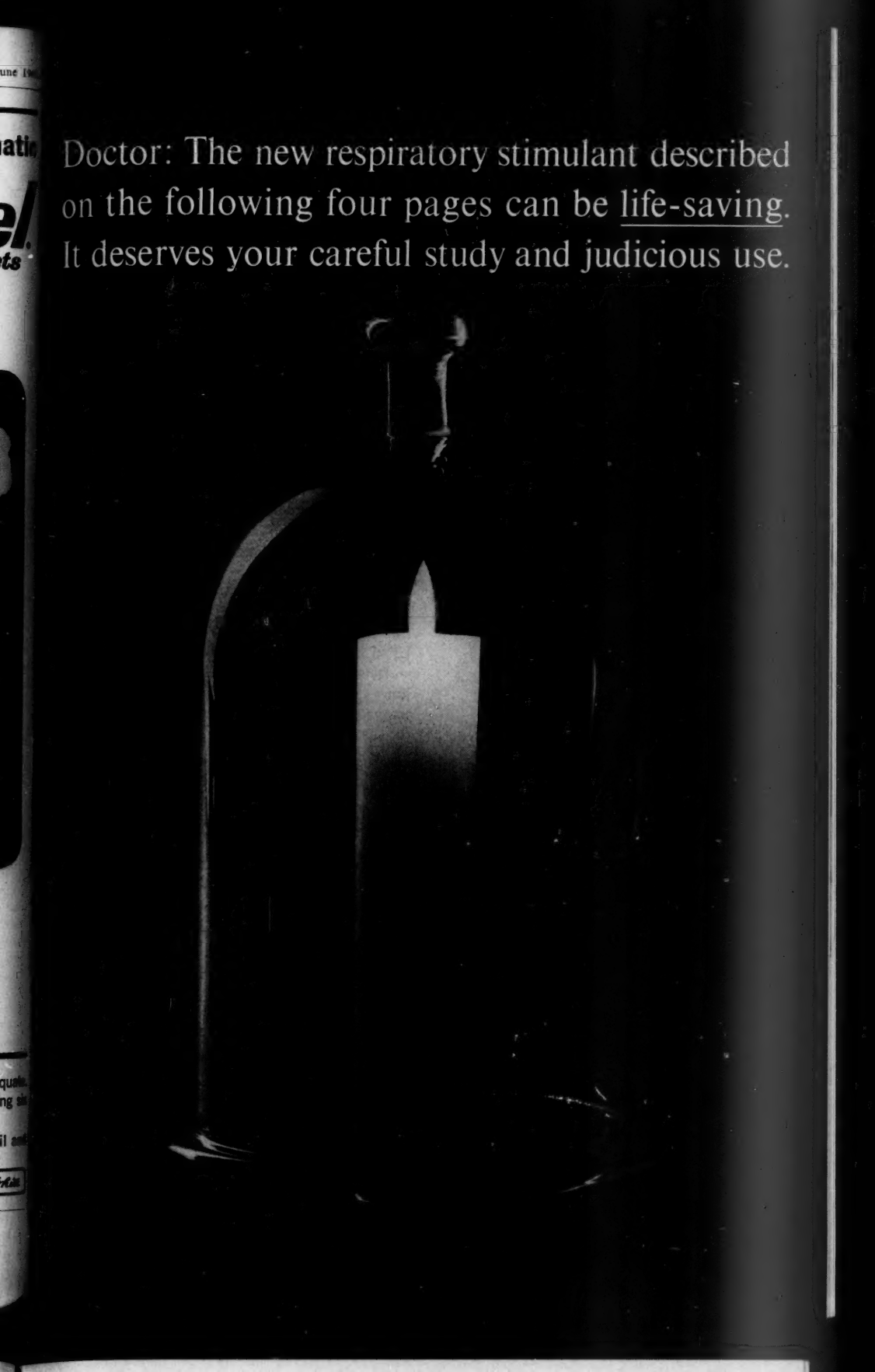
(Complete information regarding the use of Sorboquel Tablets is available on request.)

dosage: For older children and adults, initial dosage of one SORBOQUEL Tablet q.i.d. is usually adequate. Severe diarrheas may require six, or even eight, tablets in divided daily doses. (Dosages exceeding six tablets a day should not be employed over prolonged periods.)

Supplied: Sorboquel Tablets, bottles of 50 and 250. Each tablet contains 0.5 Gm. polycarbophil and 15 mg. thihexinol methylbromide.

WHITE LABORATORIES, INC., Kenilworth, New Jersey

Doctor: The new respiratory stimulant described on the following four pages can be life-saving. It deserves your careful study and judicious use.



a new respiratory stimulant and "arousing

What is Emivan?

Emivan is the diethylamide of vanillic acid (3-methoxyl-4-hydroxybenzoic acid diethylamide). Its principal action is central respiratory stimulation. Medullary center respiratory activity of the drug increases depth and to a lesser degree rate of breathing. "Arousing" effect at higher dosage has been ascribed to activity on the occipital lobes of the cerebral cortex.

Emivan is different in chemistry and in selectivity of action from other so-called "analeptic" drugs, such as nicotinic acid amides, tetrazols, amphetamines, alkaloids, or depressant-drug analogs.

When and how to use Emivan

Intravenous Emivan is used in patients with central nervous system depressant intoxication from barbiturates, sedatives, etc.; in severe respiratory and central depression caused by excessive carbon dioxide accumulation, as in pulmonary insufficiency; in "lightening" anesthesia and prevention of post-anesthesia respiratory complications.

Intravenous Emivan *does not replace,* but may be used to *supplement* the specific narcotic antagonists (levallorphan tartrate or nalorphine HCl) in the emergency treatment of narcotic intoxication.

Oral Emivan is used in the treatment or prevention of excessive CO_2 retention in patients with chronic respiratory insufficiency.

Emivan stimulates respiration with dramatic speed

Upon intravenous injection, Emivan promptly —often within 60 seconds—stimulates respiration—even in severe CNS depression, and may awaken the less severely depressed patient.

Emivan is substantially safer, and more closely approaches the "ideal" respiratory stimulating agent

(a) Since Emivan acts selectively on the respiratory center of the medulla, rather than on all medullary control centers,[1,2] at therapeutic dosage levels it does not evoke certain undesirable side reactions of so-called "analeptic" agents.

Emivan apparently has no direct effect upon cardiovascular regulatory mechanisms. No changes in cardiac rate or rhythm have been observed following its use; nor has blood pressure been significantly affected.[3-5]

Most analeptics, even at therapeutic dosage levels, may overstimulate to produce convulsions, followed by severe compensatory central depression. With Emivan, convulsion is rare, and has only followed large intravenous over-

EMIVAN is a registered trademark of the U.S. VITAMIN & PHARMACEUTICAL CORP.

EMIVAN®

BRAND OF ETHAMIVAN

response in seconds...singularly safe

- in CO_2 retention and central depression resulting from hypoventilation in pulmonary disorders, including obstructive pulmonary emphysema, cor pulmonale, etc.
- in life-threatening central nervous system depressant intoxication, as with barbiturates
- in "lightening" of general anesthesia; prevention of post-anesthetic respiratory complications

dosage, is brief in duration, quickly self-reversing, and is not followed by secondary post-convulsive depression.[3,6]

(b) Emivan dosage is easily titrated to the response of the patient, and its action readily controlled by adjusting the dose; thus it may be used in continuous intravenous infusion.

Emivan provides a "life-saving airlift" — in drug-induced depression of the central nervous system

Many drugs, such as barbiturates, non-barbiturate sedatives and hypnotics, and some tranquilizers, when taken in accidental or suicidal overdosage, cause severe depression of the central nervous system, particularly the respiratory centers. Swift reversal of this CNS depression, with stimulation of spontaneous breathing, follows intravenous administration of Emivan. (See Product Brochure for details.)

Clinical results with Emivan in CNS depressant intoxication

Bernstine and Moskal:[4] In seven patients with severe barbiturate intoxication, Emivan administered intravenously aided in complete recovery within 12 hours or less, without the need for tracheotomy. The eighth patient, a 72-year-old woman with diabetes and heart disease, who had ingested both glutethimide and barbiturates, likewise responded to Emivan I.V., with complete recovery in 60 hours. All the patients showed a marked increase in depth and rate of breathing, without side effects. The rapidity and completeness of recovery in this group were in contrast to the convulsion caused with other stimulants prior to the availability of Emivan, as well as the prolonged recovery period requiring tracheal fenestration.

Leydic and Smith:[5] 26 deeply comatose patients intoxicated with CNS depressants (principally barbiturates) were treated with intravenous Emivan. The drug was given at 5 minute intervals in an average dose of 2 mg./kg. Emivan restored and maintained spontaneous respiration and protective reflexes in all but one; and accomplished rapid and complete awakening in 15. There were no clinical signs of drug toxicity, and significant side effects were not observed.

Similar life-saving results with intravenous Emivan in CNS depressant intoxication were also reported by Cole *et al.*, in JAMA[7]; Van Gasse[8]; Baum *et al*[9]; and Miller.[10]

Emivan provides an "airlift" in respiratory depression associated with CO_2 accumulation resulting from hypoventilation

Emivan temporarily increases ventilation, and thus aids in the removal of excess carbon diox-

(continued)

ide accumulating as a result of obstructive pulmonary defects. Boren[11] first pointed out that Emivan was an effective respiratory stimulant in the presence of severe respiratory acidosis. He demonstrated increased minute ventilation following 50 to 100 mg. of Emivan I.V. given over a period of one minute. Both volume and, to a lesser degree, rate of breathing were increased, despite the presence of markedly elevated blood-CO_2 levels and respiratory depression. These results were observed in patients with obstructive pulmonary defects, including pulmonary emphysema with bronchitis, cor pulmonale, and bronchogenic carcinoma. In cases of severe CO_2 narcosis, intravenous Emivan overcame the apneic response to 100% oxygen breathing.[3] Boren found also, that in those patients who had responded to intravenous Emivan with improvement in ventilation and elimination of excess CO_2, *oral* Emivan, given in doses of 20 to 40 mg., usually q.i.d., for periods ranging from one to five days up to five to eight weeks, effected gradual improvement during acute episodes of hypoventilation. Eventually this permitted withdrawal of the oral drug. All of these patients had severe pulmonary emphysema, and it was noted that in acute episodes of infection, "Emivan added to other forms of therapy was probably a big factor in allowing survival . . ."[3]

Baum *et al.*[9] giving Emivan by intravenous infusion, recorded significant increases in minute ventilation (average 2.5 liters per minute) with corresponding reduction in arterial Pco_2 (average 4.1 mm. Hg). Evidence was also obtained that respiratory-center sensitivity to CO_2 stimulus is increased during Emivan administration, and the improvement in tolerance to oxygen breathing in emphysema patients with CO_2 retention was confirmed.

Miller[10] found Emivan effective, by both intravenous and oral routes, as a stimulant to respiration in hypoventilation with CO_2 retention in chronic pulmonary disease and in obesity. An increase in the rate and depth of respiration was noted within 30 to 90 seconds after the intravenous administration of 50 to 100 mg. of Emivan in these patients. Fisherman[12] has also used oral Emivan, with improvement in respiration in 11 patients (8 with advanced pulmonary emphysema, and 3 with emphysema complicating severe intrinsic bronchial asthma).

Emivan conveniently "lightens" anesthesia—shortens recovery room time—helps prevent post-anesthesia respiratory complications

According to Adriani,[13] "There is little justification for allowing a patient to remain in a comatose, areflexive state when there is a possibility that reflex activity may be elevated and the sensorium cleared to the point where one may dispense with tracheotomy, artificial respiration and constant attendance by physicians and nurses." The primary effect of general anesthesia is CNS depression; in particular, the nervous control of respiration as well as alveolar and exchange phases are of prime concern. Adequate ventilation to remove excess CO_2 becomes essential in post-anesthesia, post-operative care. Emivan is valuable—alone or as an adjunct to mechanically assisted breathing, in producing adequate ventilatory response, thus preventing post-anesthesia respiratory problems. When the anesthesiologist wishes to "lighten" general anesthesia, Emivan is prompt in awakening the anesthetized patient; restoring consciousness, voluntary responses, and easy spontaneous respiration; and improving general muscle tone.

Clinical results with Emivan in "lightening" anesthesia

Leydic and Smith:[5] Emivan was evaluated preliminarily as an anesthesia-"lightening" agent, following surgery in 350 cases. Duration of surgery ranged from 15 minutes to 8 hours, with an average of 2½ hours. "Definite arousal" was produced within 35 to 60 seconds in 74 percent of this series after a single slow intravenous injection of 2 mg./kg. of Emivan. The remainder responded after one or two additional injections at short intervals. There was an abrupt increase in minute volume of respiration, a return of corneal reflex, swallowing, motor response (rubbing of nose or mouth), and appropriate response to simple commands.

Byers[14] administered 2 mg./kg. of Emivan intravenously to 72 cases immediately after surgery, in which Surital alone, or with nitrous

oxide or cyclopropane and Anectine®, had been the anesthetic agent. "The awakening or arousing effect was dramatic," reported this investigator. Respiratory rate and volume increased markedly for a brief period. In only 11 patients was a second dose needed.

Slater:[15] Oral surgery was performed on 58 ambulatory patients, ranging in age from 3 to 50 years, under various anesthetics. Emivan proved to be "an excellent respiratory and CNS stimulant with very little undesirable side effects." Slater also noted that "Emivan has its greatest use in the recovery room by reducing significantly the length of stay for the patient," thereby economizing on staff duty time. Average time from general anesthesia to ambulatory state was 15 minutes in these cases.

Side effects

Depending upon the speed of intravenous injection, or the oral dosage used for a given level of central depression, certain transient side effects may at times be encountered. These may include: coughing, sneezing, laryngospasm, muscular twitching, itching, other pruritic manifestations, flushing and lightheadedness. In many instances, these reactions, particularly the protective reflex stimuli to breathing, coughing and sneezing, have a positive value as signposts to the progress of recovery of the patient.

Consult product brochure for administration, dosage, complete precautions and contraindications

Should coughing or sneezing endanger the immediate post-operative course of the anesthetized surgical patient (delicate ophthalmic surgery, repair of retinal detachment, etc.), Emivan should be used with great caution or not at all.

SUPPLIED: 2 cc. ampuls containing 100 mg. of vanillic diethylamide and 10 cc. ampuls containing 500 mg. of vanillic diethylamide in 5% aqueous diethanolamine solution, for intravenous injection or infusion with intravenous fluids. 2 cc. ampuls, boxes of 5, 25, and 100; 10 cc. ampuls, boxes of 1, 5 and 25.

Tablets (uncoated) providing 20 mg. of vanillic diethylamide for oral use. Bottles of 100 and 500.

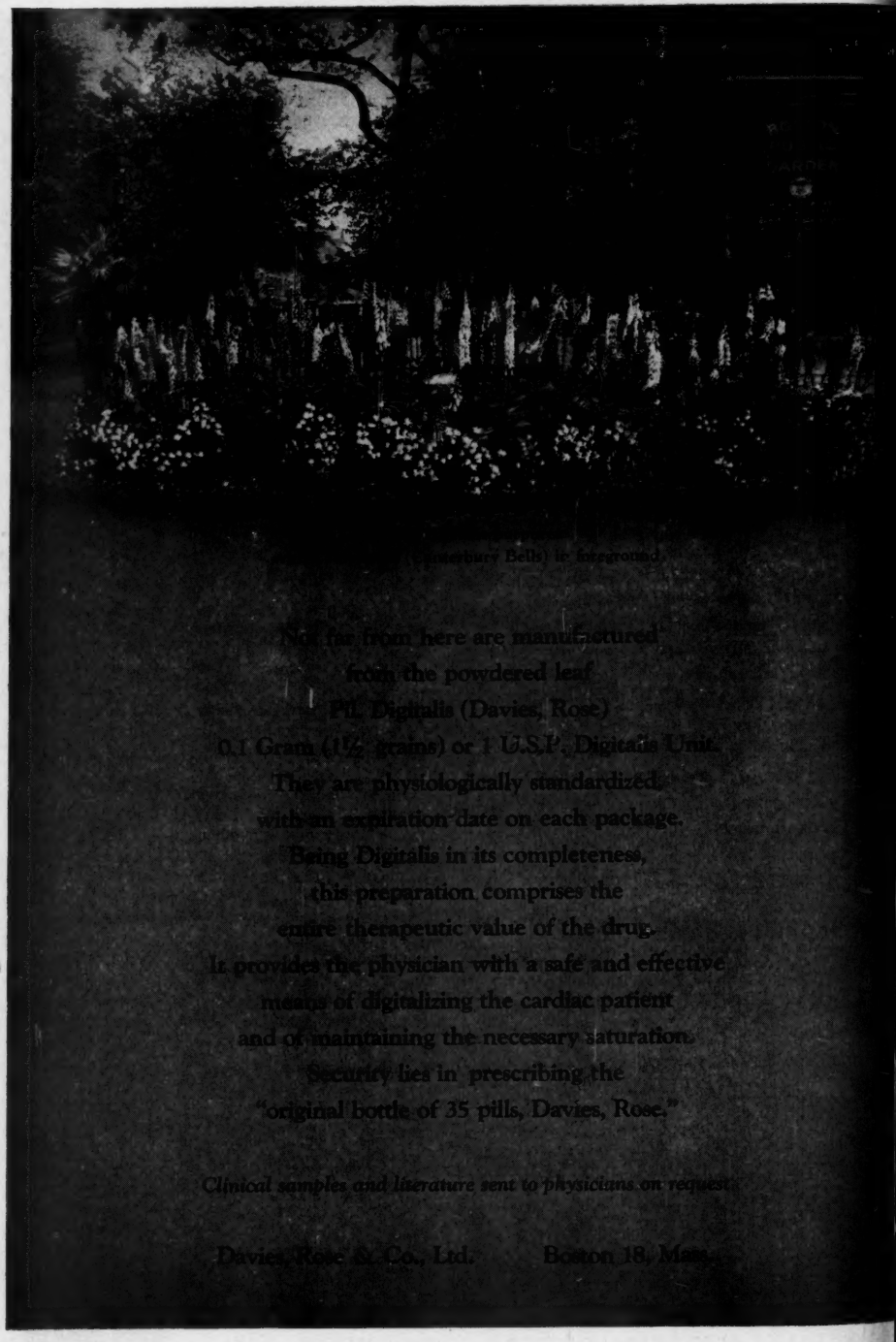
REFERENCES: 1. Ginzel, K. H.: Wien. Ztschr. inn. Med. *33*:16, 1952. 2. Buckley, J. P.: Personal Communications, March 21, 1960. 3. Boren, H. G.: Clinical use of vanillic diethylamide (Emivan) as a respiratory stimulant. In press. 4. Bernstine, M. L., and Moskal, J. P.: Anesthesiology *21*:90 (Jan.-Feb.) 1960. 5. Leydic, C. C., Jr., and Smith, H. D.: Clinical Report on file at U.S. Vitamin & Pharmaceutical Corporation. 6. Miller, M. J.; Hand, B. M., and Crellin, J. A.: Preliminary report on the clinical use of vanillic diethylamide. Presented at Annual Meeting, American Therapeutic Society, Miami Beach, Florida (June) 1960. 7. Cole, G. W.: Marks, A., and Baum, G. L.: J.A.M.A. *174*:896 (Oct. 15) 1960. 8. Van Gasse, J. J.: Detailed reports on file at U.S. Vitamin & Pharmaceutical Corporation. 9. Baum, G. L.; Hagedorn, G.; Rosenstein, I. A., and Silipo, S.: Experiences with Emivan, a new respiratory stimulant. Presented at 17th Annual Meeting, American College of Chest Physicians, St. Louis, Mo., October 1960. 10. Miller, W. F.: (a) Clinical Report on file at U.S. Vitamin & Pharmaceutical Corporation. (b) Scientific exhibit presented at A.M.A. Annual Meeting, Miami Beach, Florida, June 13-17, 1960. 11. Boren, H. G.: M. Clin. North America, *43*:33 (Jan.) 1959. 12. Fisherman, E. W.: Personal Communication, Jan. 22, 1960. 13. Adriani, J.: Postgrad. Med. *27*:723 (June) 1960. 14. Byers, R. J.: Personal Communication, January 26, 1960. 15. Slater, H. M.: Vanillic diethylamide (Emivan) for post-anesthetic recovery, report presented at 16th Annual Meeting Western Division Canadian Anesthetic Society, Winnipeg, Manitoba, March 9, 1961.

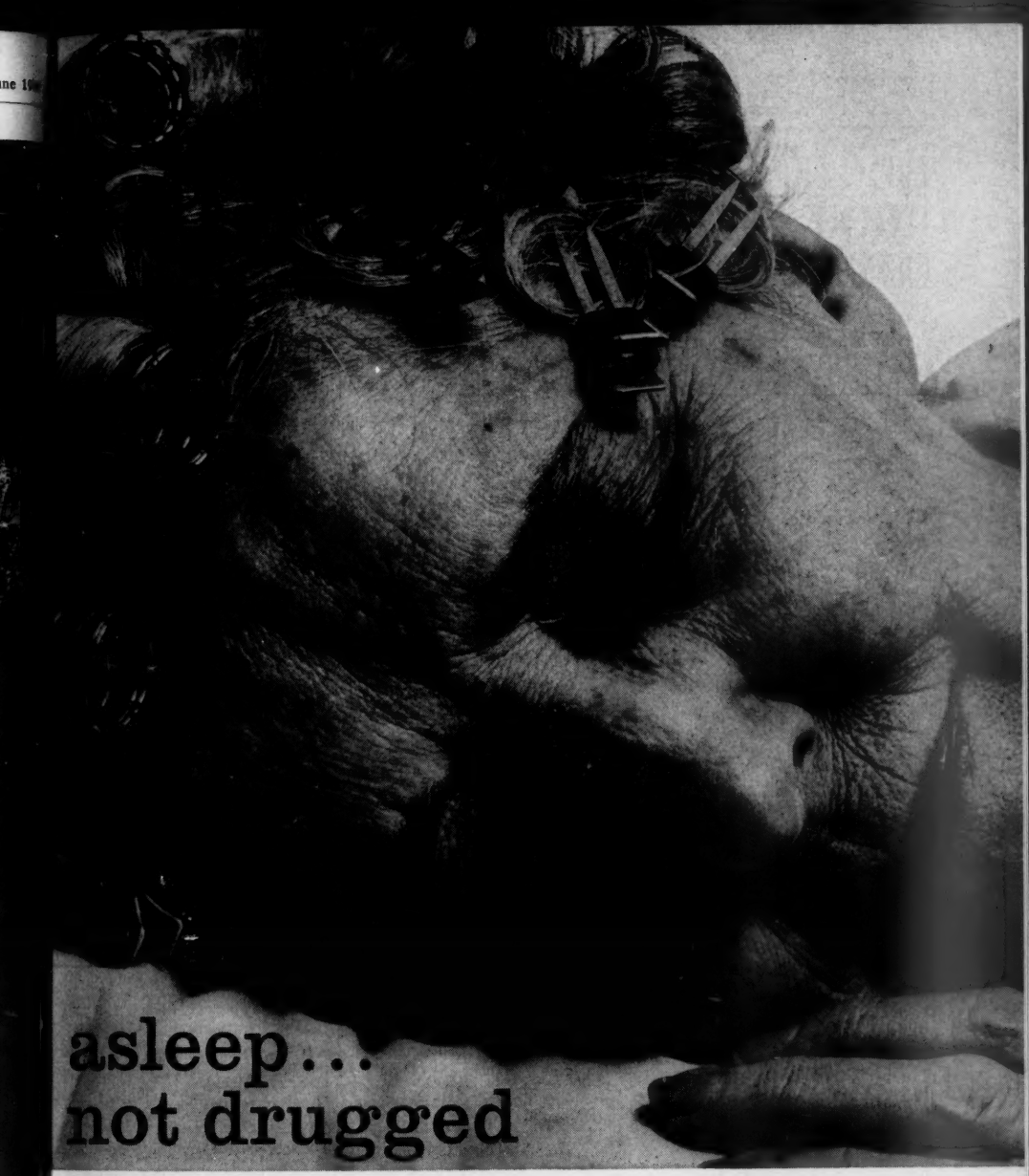
a new respiratory stimulant and "arousing" agent...response in seconds, singularly safe

EMIVAN



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(Canterbury Bells) in foreground
Not far from here are manufactured
from the powdered leaf
Pil. Digitalis (Davies, Rose)
0.1 Gram (1½ grains) or 1 U.S.P. Digitalis Unit.
They are physiologically standardized
with an expiration date on each package.
Being Digitalis in its completeness,
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entire therapeutic value of the drug.
It provides the physician with a safe and effective
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Security lies in prescribing the
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For a night of deep, refreshing sleep and a lively awakening... Noludar 300... one capsule at bedtime promises 6 to 8 hours of undisturbed sleep without risk of habituation, without barbiturate "hangover," toxicity or even minor side effects. Try Noludar 300 for your next patient with a sleep problem. One capsule at bedtime. Chances are she'll tell you

"I slept like a log"

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300-mg capsules

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BECAUSE POOR DIABETIC CONTROL INCREASES THE THREAT OF VASCULAR COMPLICATIONS IN DIABETES[1, 2]...
DIABINESE FIRST FOR ADEQUATE AND CONTINUOUS ORAL CONTROL

Oral therapy with DIABINESE can help assure more adequate blood-sugar control in many maturity-onset diabetics, including certain patients now poorly controlled by diet alone, some patients on insulin, and many who escape control on previous oral therapy.

Diabinese and diet

In patients with maturity-onset diabetes whose blood sugar remains elevated despite weight and/or calorie control, DIABINESE is frequently effective in doses of 100 to 250 mg. a day. Further, unlike insulin, DIABINESE has not been reported to increase appetite, and residual capacity for endogenous beta cell activity is stimulated. Thus, DIABINESE combined with dietary regulation will often ensure more satisfactory control than "diet alone."

Diabinese and the insulin patient

DIABINESE has proved to be an effective replacement for insulin among maturity-onset patients needing 40 units or less per day. This application of DIABINESE is especially valuable in patients who should not be exposed to the hazards and inconvenience of self-administered injection—those with poor eyesight, the infirm and elderly, and the emotionally disturbed. Transfer from insulin to DIABINESE in proper dosage lessens the risk of hypoglycemia, and may enable certain patients to resume occupations where insulin shock is considered dangerous.

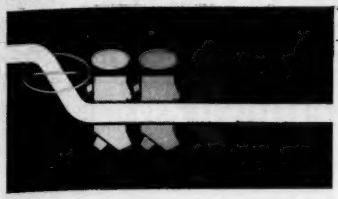
In selected patients in whom insulin requirements have become quite high, combined therapy with DIABINESE sometimes permits reduction of insulin dosage and helps to improve control.[3] Patients with insulin resistance may sometimes be similarly helped by replacement of part of the daily insulin dosage.[4]

Diabinese from the start

Continuous control in suitable candidates for sulfonylurea therapy is more likely to be achieved with DIABINESE. According to the A.M.A. Council on Drugs,[5] observations indicate that "on an equivalent dose and blood level basis, chlorpropamide has a somewhat greater therapeutic effect than has tolbutamide." This therapeutic superiority is reflected in the results of clinical observations like those of Fineberg,[6] who compared the effect of DIABINESE in 50 patients with the effect of tolbutamide in 35 patients. He concluded that "chlorpropamide produced satisfactory control of the diabetes in almost twice as great a percentage (76 versus 43 per cent) of patients than did tolbutamide, and excellent control in more than twice as great a percentage (74 versus 31 per cent)."

1. Johnsson, S.: Diabetes 9:1, 1960. 2. El Mahallawy, M. N., and Sabour, M. S.: J.A.M.A. 173:1783, 1960. 3. Editorial: Brit. M. J. 1:188, 1961. 4. Duncan, L. J. P., and Baird, J. D.: Pharmacol. Rev. 12:91, 1960. 5. A.M.A. Council on Drugs: New and Nonofficial Drugs, 1961, Philadelphia, Lippincott, 1961, p. 657. 6. Fineberg, S. K.: J. Am. Geriat. Soc. 8:441, 1960.

FOR MAXIMUM ASSURANCE OF CONTINUOUS BLOOD-SUGAR CONTROL



Diabinese® *the oral antidiabetic most likely to succeed*

BRAND OF CHLORPROPAMIDE

economical once-a-day dosage

IN BRIEF

DIABINESE, a potent sulfonylurea, provides smooth, long-lasting control of blood sugar permitting economy and simplicity of low, once-a-day dosage. Moreover, DIABINESE often works where other agents have failed to give satisfactory control.

INDICATIONS: Uncomplicated diabetes mellitus of stable, mild or moderately severe nonketotic, maturity-onset type. Certain "brittle" patients may be helped to smoother control with reduced insulin requirements.

ADMINISTRATION AND DOSAGE: Familiarity with criteria for patient selection, continued close medical supervision, and observance by the patient of good dietary and hygienic habits are essential.

Like insulin, DIABINESE dosage must be regulated to individual patient requirements. Average maintenance dosage is 100-500 mg. daily. For most patients the recommended starting dose is 250 mg. given once daily. Geriatric patients should be started on 100-125 mg. daily. A priming dose is not necessary and should not be used; most patients should be maintained on 500 mg. or less daily. Maintenance dosage above 750 mg. should be avoided. Before initiating therapy, consult complete dosage information.

SIDE EFFECTS: In the main, side effects, e.g., hypoglycemia, gastrointestinal intolerance, and neurologic reactions, are related to dosage. They are not encountered frequently on presently recommended low dosage. There have been, however, occasional cases of jaundice and skin eruptions primarily due to drug sensitivity; other side effects which may be idiosyncratic are occasional diarrhea (sometimes sanguineous) and hematologic reactions. Since sensitivity reactions usually occur within the first six weeks of therapy, a time when the patient is under very close supervision, they may be readily detected. Should sensitivity reactions be detected, DIABINESE should be discontinued.

PRECAUTIONS AND CONTRAINDICATIONS: If hypoglycemia is encountered, the patient must be observed and treated continuously as necessary, usually 3-5 days, since DIABINESE is not significantly metabolized and is excreted slowly. DIABINESE as the sole agent is not indicated in juvenile diabetes mellitus and unstable or severely "brittle" diabetes mellitus of the adult type. Contraindicated in patients with hepatic dysfunction and in diabetes complicated by ketosis, acidosis, diabetic coma, fever, severe trauma, gangrene, Raynaud's disease, or severe impairment of renal or thyroid function. DIABINESE may prolong the activity of barbiturates. An effect like that of disulfiram has been noted when patients on DIABINESE drink alcoholic beverages.

SUPPLIED: As 100 mg. and 250 mg. scored chlorpropamide tablets.

More detailed professional information available on request.

Science for the world's well-being® Pfizer PFIZER LABORATORIES
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Proven

in over six years of clinical use and more than 750 published clinical studies

Effective

for relief of anxiety and tension

Outstandingly Safe

1. simple dosage schedule produces rapid, dependable tranquilization without unpredictable excitation
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Miltown®

meprobamate (Wallace)

Usual dosage: One or two 400 mg. tablets t.i.d.
Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets; in bottles of 50.

Also supplied in sustained-release capsules . . .

Meprospan®

Available as Meprospan-400 (blue-topped *sustained-release* capsules containing 400 mg. meprobamate), and Meprospan-200 (yellow-topped *sustained-release* capsules containing 200 mg. meprobamate).

CM-4234

WALLACE LABORATORIES / *Cranbury, N. J.*

Arrest the Coughs that Steal Sleep...

CHRONIC SINUSITIS

PHARYNGITIS

INFLUENZA-COLDS

BRONCHITIS

CHRONIC LUNG DISEASE

CARDIAC DECOMPENSATION

MEASLES



Prescribe

TUSSIONEX®

A 'Strasionic' Antitussive • Dihydrocodeinone Resin—Phenyltoloxamine Resin

8-12 Hour Cough Control with a Single Dose

- **Permits Natural Discharge of Mucus**
- **Predictable Antitussive Action with Minimum Amount of Narcotic through 'Strasionic' Release**

TWO FORMS: Tussionex Thixaire™ Suspension • Tussionex Tablets

Each teaspoonful (5c.c.) or tablet provides 5 mg. dihydrocodeinone and 10 mg. phenyltoloxamine as resin complexes.

Dose: 1 teaspoonful or tablet q12h. Children under 1 year, ¼ teaspoonful q12h; 1-5 years, ½ teaspoonful q12h.

Rx only. Class B taxable narcotic.

Tussionex—made and marketed only by

STRASENBURGH

Her hunger



s "liquidated"... but her appetite survives!

Mealtime *hunger* reflects a physiological need quickly satisfied by food—liquid or solid.

But *appetite* represents a psychological need which is often the obese patient's biggest problem. Measures that satisfy hunger alone are not enough. Mealtimes rapidly become tedious on unnatural diets... and high calorie snacks, between-meal nibbling, and refrigerator raiding provide an appetizing consolation! When appetite survives, willpower soon vanishes.

You can help her *satisfy* her *appetite* as well as her hunger... and still be sure of

SUSTAINED WEIGHT CONTROL

by prescribing Biphetamine or Ionamin. A single capsule dose appeases appetite for 10-14 hours. Your patient enjoys normal food (in lesser quantities) while better eating habits and proper weight are gradually established and maintained.

If She's "Sedentary"

BIPHETAMINE®
A 'STRASIONIC' ANORETIC RESIN

BIPHETAMINE '20'
(20 mg.)

BIPHETAMINE '12½' (12.5 mg.) **BIPHETAMINE '7½'** (7.5 mg.)

Each capsule of each strength contains equal parts of d-amphetamine and dl-amphetamine as cation exchange resin complexes of sulfonated polystyrene.

If She's "Active"

IONAMIN®
A 'STRASIONIC' ANORETIC PHENTERMINE RESIN

IONAMIN '30'
(30 mg.)

IONAMIN '15'
(15 mg.)

Each capsule of each strength contains phentermine as a cation exchange resin complex of sulfonated polystyrene.

If She's "Refractory"

NEW **BIPHETAMINE-T®**
A 'STRASIONIC' ANORETIC RESIN

BIPHETAMINE-T '20' **BIPHETAMINE-T '12½'**

Each capsule of each strength contains Tuazole® and equal parts of d-amphetamine and dl-amphetamine—all as cation exchange resin complexes of sulfonated polystyrene.

Single Capsule Daily Dose 10 to 14 hours before retiring

STRASENBURGH

"On the Way"...

WITH AKALON®-T

'STRASIONIC' ANTICHOLINERGIC METHSCOPOLAMINE-TUAZOLE® RESIN



Just 2 Capsules a Day

Heartburn
Hyperacidity
Painful Spasm
Nocturnal Pain
Gastroenteritis
Peptic Ulcer



A single capsule dose Akalon-T calms the GI tract, combats hypersecretion of pepsin as well as acid for 8-12 hours. Release of Akalon-T is uniform and predictable, since it is unaffected by fluctuations in pH, enzymatic activity, or motility. Your patient is "on the way" with just 2 capsules a day.

'Strasionic' release makes the BIG difference



AKALON-T '5': 5 mg. Methscopolamine and 20 mg. Tuazole (Brand of 2-methyl-3-orthotolyl-quinazolone) as cation exchange resin complexes of sulfonated polystyrene.



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Akalon-T—made and marketed ONLY by **STRASENBURGH**

We use the new easy accurate way to test basal metabolism



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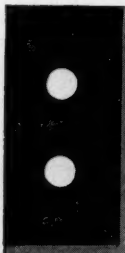
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Over 600,000,000 patient-days of effective, well-tolerated antihypertensive therapy...

Rauwiloid®

alseroxylon, 2 mg.

is still unexcelled

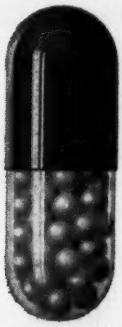


Just two tablets at bedtime

Eight years of continuous use... prove enduring patient-acceptance and physician-satisfaction with RAUWILOID...*without any revisions of claims, changes of dosage, or additional side actions encountered.*

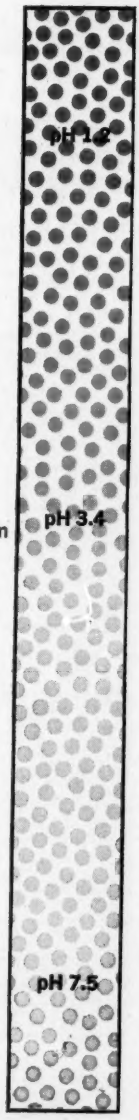
Rauwiloid is an original development of Riker Northridge, California

135 tiny doses mean smoother steroid therapy...



in acute allergic disorders:

In the relatively acid medium of the fasting stomach, Medrol Medules remain essentially intact —only 5% of the Medrol content is released after 2 hours at pH 1.2. However, in the environment of the duodenum (approaching a pH of 7.5), from 90 to 100% of the Medrol is released over a period of 4 hours.



Judged to be "a nearly ideal formulation,"[1] Medrol Medules gave good to excellent results in 25 of 28 children with various acute allergic disorders. "There were no serious side effects and minor complaints were reported in only two patients."[1] The author also found that "there is a definite advantage for Medrol Medules inasmuch as much smaller doses seem able to produce full clinical relief. . . ."[1]

Indications and effects

Medrol benefits (anti-inflammatory, antiallergic, antirheumatic, antileukemic, antihemolytic) have been demonstrated in acute rheumatic carditis, rheumatoid arthritis, asthma, hay fever and allergic disorders, dermatoses, blood dyscrasias, and ocular inflammatory disease involving the posterior segment.

Precautions and contraindications

Because of Medrol's high therapeutic ratio, patients usually experience dramatic relief *without* developing such possible steroid side effects as gastrointestinal intolerance, weight gain or weight loss, edema, hypertension, acne, or emotional imbalance.

As in all corticotherapy, however, there are certain cautions to be observed. The presence of diabetes, osteoporosis, chronic psychotic reactions, predisposition to thrombophlebitis, hypertension, congestive heart failure, renal insufficiency, or active tuberculosis necessitates careful control in the use of steroids. Like all corticosteroids, Medrol is contraindicated in patients with arrested tuberculosis, peptic ulcer, acute psychoses, Cushing's syndrome, herpes simplex keratitis, vaccinia, or varicella.

1. Dugger, J. A.: J. Michigan M. Soc. *59*:1812 (Dec.) 1960.

Medrol* Medules†

Each capsule contains: Medrol (methylprednisolone) 4 mg.

Supplied in bottles of 30 and 100.

Upjohn

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GOUT

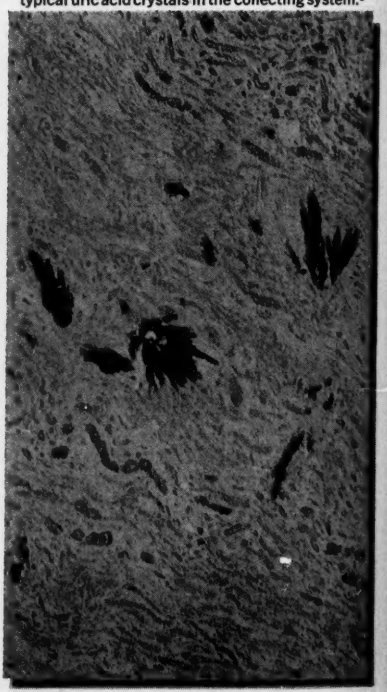
"For centuries the victims of gout have been the subject of lampoons and caricatures. We now know that they should rather be the objects of great concern, for the disease is painful, disabling and is accompanied by complications that impair health and shorten life."[1]

Kidney impairment, with varying degrees of hypertension and arteriosclerosis, is the critical complication of gout. "From 30 to 50 per cent of gouty patients are said to die of renal disease."[2]

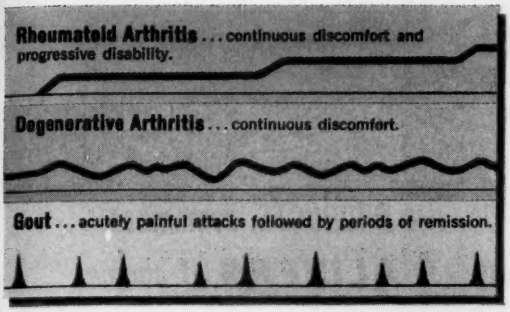
Tophus in the calyx, surrounded by fibrinoid exudate and detached mucosal epithelium.[3]

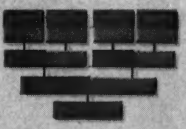


The mid- and outer portion of the pyramid with typical uric acid crystals in the collecting system.[3]



AIDS TO DIAGNOSIS





"If a family history of gout is obtained, even though it is one or two generations removed, this information is significant."[4]



"The metatarsophalangeal joint of a great toe is affected early or repeatedly in some cases, rarely or never in others."[6]



"All patients complaining of non-traumatic musculoskeletal discomfort should have at least one serum uric acid determination."[5]



Colchicine test: "Colchicine should be administered as early as possible after the onset of articular distress, 1 mg.... every 2 hours until the onset of gastro-intestinal distress. From 5 to 8 mg. usually are required."[9] Pain relief is highly indicative of gout.

THE "INSULIN OF GOUT"[7]

"Of the various drugs with uricosuric activity, probenecid [BENEMID] has proved most desirable for long-term administration."[8]

BENEMID®

PROBENECID

Therapy with BENEMID should be continued without interruption since hyperuricemia recurs when dosage is terminated. The rare patient who experiences gastric discomfort is usually benefited by decreasing the dosage. Dosage: 0.25 Gm. twice daily for one week, followed by 1 Gm. daily in divided doses. Supply: 0.5 Gm. tablets.

A COMPLEMENTARY FORMULATION OF TWO CLASSIC ANTI-GOUT AGENTS

"... the greater the experience we have with the combination of colchicine and Benemid the greater the reliance we place upon these two drugs."[9]

ColBENEMID®

COLCHICINE WITH BENEMID

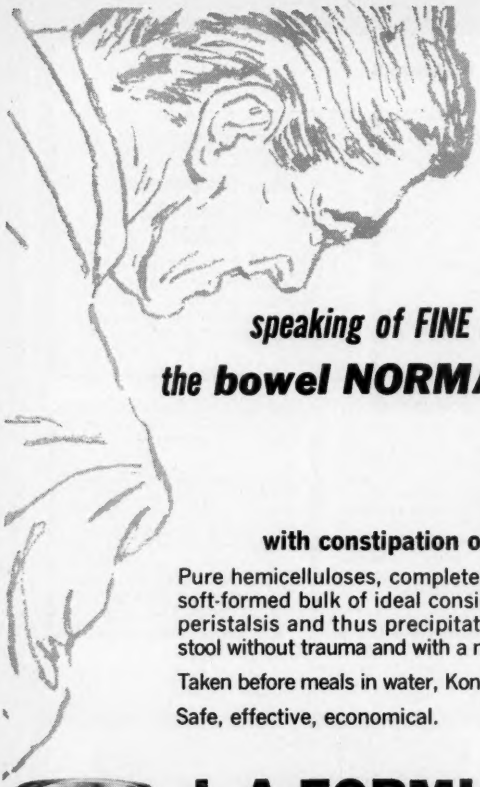
Dosage: One tablet daily for one week, followed by one tablet twice daily. Supply: Each tablet contains 0.5 mg. colchicine and 0.5 Gm. BENEMID. Bottles of 100 and 1000.

1. Cornish, A. L.: J. Kentucky M.A. 58:707, June, 1960. 2. Wyngaarden, J. B.: Arthritis & Rheumatism 1:191, June, 1958. 3. Talbott, J. H. and Terplan, K. L.: Medicine 39:405, Dec., 1960. 4. Talbott, J. H.: Gout, New York, Grune & Stratton, 1957, p. 123. 5. Kuzell, W. C., et al.: J. Chron. Dis. 2:645, Nov., 1955. 6. Hench, P. S.: Gout and gouty arthritis, in Cecil, R. L.: A textbook of medicine, ed. 10, Phila., W. B. Saunders Co., 1959. 7. Bartels, E. C., and Kepkay, P. H.: Bull. Vancouver M.A. 29:306, April, 1953. 8. Boland, E. W.: World-Wide Abstracts of Gen. Med. 3:16, Jan., 1960. 9. Talbott, J. H.: Current Med. Dig. 26:57, Nov., 1959.

Before prescribing or administering BENEMID or ColBENEMID, the physician should consult the detailed information on use accompanying the package or available on request.

MSD MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.

BENEMID AND COLBENEMID ARE TRADEMARKS OF MERCK AND CO., INC.



speaking of FINE PRODUCTS, remember
the ***bowel NORMALIZERS*** *of choice....*

KONSYL

for the obese patient
with constipation or non-specific diarrhea



Pure hemicelluloses, completely calorie-free, producing a soft-formed bulk of ideal consistency to stimulate normal peristalsis and thus precipitate easy passage of a bland stool without trauma and with a minimum of peri-anal soiling.

Taken before meals in water, Konsyl helps to depress appetite.

Safe, effective, economical.



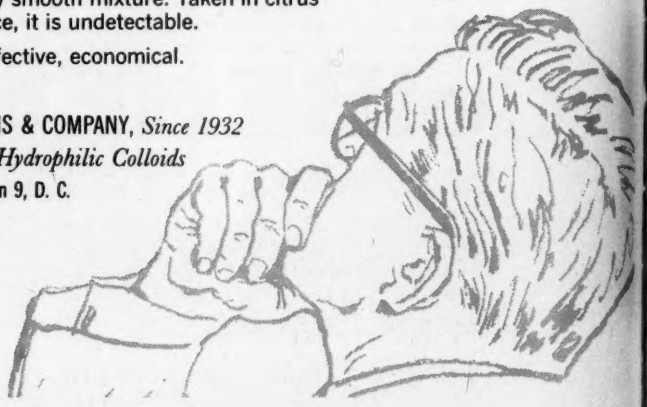
L.A.FORMULA

for the thin, finicky patient
with constipation or non-specific diarrhea

Pure hemicelluloses, ultra-pulverized to unique particle size and simultaneously dispersed in highest-grade lactose and dextrose to insure unsurpassed palatability, likewise acting to precipitate easy passage of soft formed stools for maximum relief of abnormal bowel function.

Taken in water or milk, L. A. Formula makes a velvety smooth mixture. Taken in citrus fruit juice, it is undetectable.

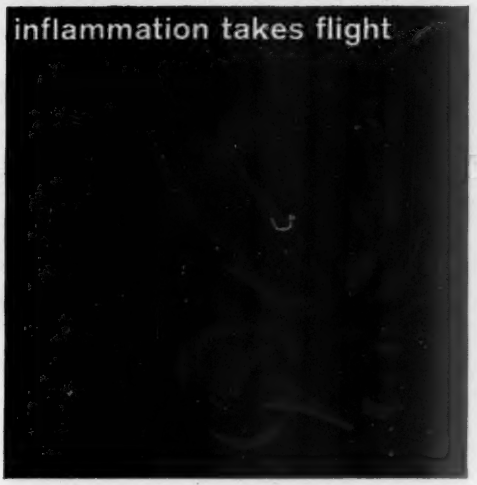
Safe, effective, economical.



Made by **BURTON, PARSONS & COMPANY,** *Since 1932*
Originators of Fine Hydrophilic Colloids
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new Tandearil Geigy

brand of oxyphenbutazone



a new development in nonhormonal, anti-inflammatory therapy

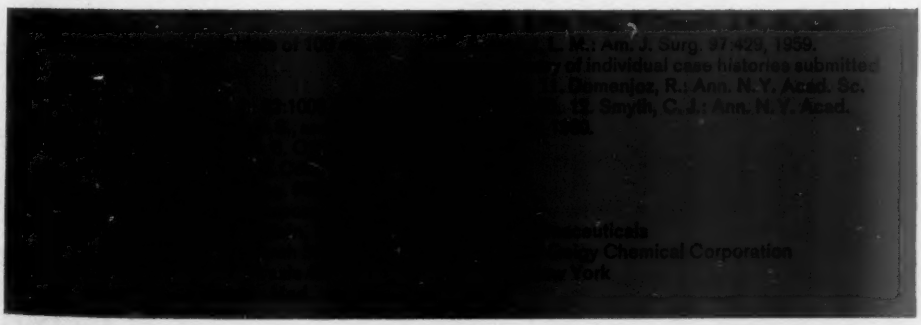
more specific than steroids—
Acts directly on the inflammatory lesion **without** altering pituitary-adrenal function . . . **without** impairing immunity responses.[6,11]

more dependable than enzymes—
Rapid and complete absorption, without the uncertainty of oral or buccal enzyme therapy.[8]

more potent than salicylates—
Anti-inflammatory potency of Tandearil markedly superior to aspirin.[12]

Remarkably useful in a wide variety of inflammatory conditions, including: rheumatoid arthritis, spondylitis, osteoarthritis[1,2,3]; gout[1,4,5]; acute superficial thrombophlebitis[6,7]; painful shoulder (peritendinitis, capsulitis, bursitis, and acute arthritis of that joint)[1,4]; severe forms of a variety of local inflammatory conditions[6,9,10].

The physician should be thoroughly familiar with the dosage, side effects, precautions and contraindications of Tandearil before prescribing. Full product information available on request.



Two exclusive developments of Roche Research

LIBRIUM the successor to the tranquilizers

helps control the anxiety and tension so frequently associated with gastrointestinal disorders—without causing drowsiness

may be used with confidence: does not cause diarrhea or other undesirable effects in the digestive tract

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Each Librax capsule provides

5 mg Librium hydrochloride and 2.5 mg Quarzan bromide.

Consult literature and dosage information, available on request, before prescribing.

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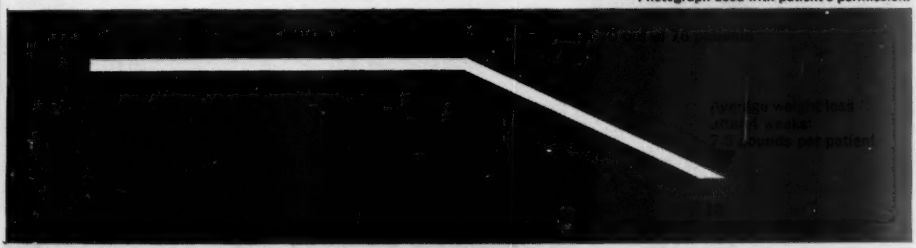


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Recent studies show that the diuretic action of Esidrix improves results of weight-reducing programs 2 ways:

1. As an adjuvant in initiating treatment: Esidrix induces greater weight losses in the first few days than a conventional regimen.[1] This weight loss may be significant in itself (depending on the degree of fluid retention). But more than that, the quick loss of even a few pounds builds confidence in the weight-reducing program, inspires determination to follow it faithfully.

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(Adapted from Einhorn and Kalb[2])

Esidrix®
(hydrochlorothiazide CIBA)

For complete information about Esidrix and Esidrix-K (including dosage, side effects, and cautions), see Physicians' Desk Reference, or write CIBA, Summit, N. J.

References: 1. Ray, R. E.: To be published. 2. Einhorn, H. P., and Kalb, S. W.: Clin. Med. 7:1995 (Oct.) 1960.

Supplied: ESIDRIX Tablets, 25 mg. (pink, scored) and 50 mg. (yellow, scored). ESIDRIX-K Tablets 25/500 (white, coated), each containing 25 mg. Esidrix and 500 mg. potassium chloride. **NEW STRENGTH ESIDRIX-K NOW AVAILABLE:** ESIDRIX-K Tablets 50/1000 (white, coated), each containing 50 mg. Esidrix and 1000 mg. potassium chloride.

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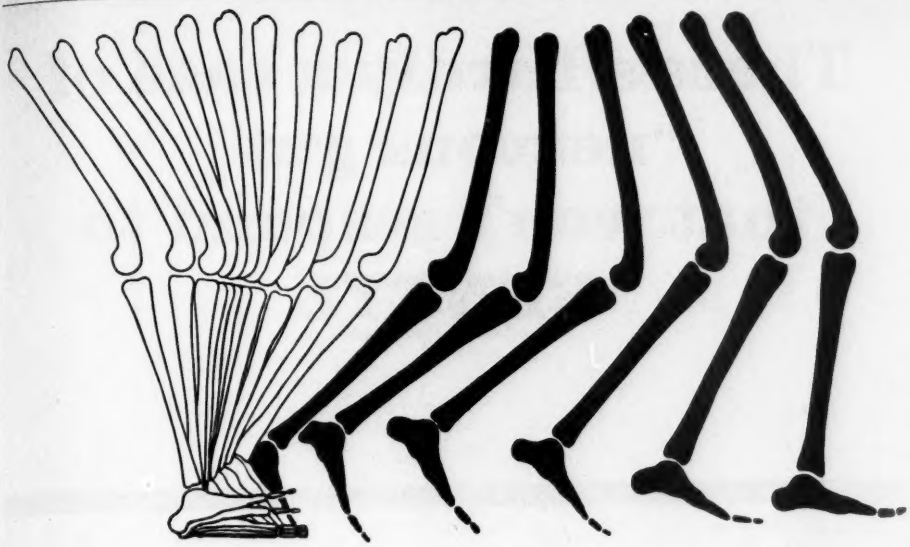
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Depo-Medrol was administered intra-articularly to 118 patients (250 injections) for disorders including rheumatoid arthritis, osteoarthritis, epicondylitis, and tendinitis.

Relief of pain and swelling was marked or complete in 104 of the 118 (88.1%); duration of response to a single injection was more than three weeks in 89 patients (75.4%) and more than six weeks in 39 of these.[1] "Post-injection flare-up was practically non-existent."[1]

Indications and dosages

Intra-articular, intrabursal and intratendinous injections of Depo-Medrol are useful for sustained anti-inflammatory effect and symptomatic relief in rheumatoid arthritis, osteoarthritis, bursitis, tendinitis, epicondylitis and other rheumatic disorders.

Intra-articular dosage depends on the size of the joint and the severity of the condition. Injections may be repeated, if necessary, at intervals of one to five weeks. A suggested dosage guide: Large joint, 20 to 80 mg.; medium joint, 10 to 40 mg.; small joint, 4 to 10 mg.

For administration directly into bursae, dosage may be 4 to 30 mg. (repeat injections are usually not needed).

For injection into the tendon sheath, 4 to 30 mg. is a usual range (in recurrent or chronic conditions, repeat injections may be needed).

Precautions

Depo-Medrol for local effect is contraindicated in the presence of acute infectious conditions. Infrequently, atrophic changes in the dermis may form shallow depressions in the skin at the injection site, but these usually disappear in a few months.

Depo-Medrol 40 mg. per cc.
Each cc. contains:

Medrol (methylprednisolone) acetate	40 mg.
Polyethylene glycol 4000	29 mg.
Sodium chloride	8.7 mg.
Myristyl-gamma-picolinium chloride	0.19 mg.
Water for injection	q.s.

Supplied: 1 cc. and 5 cc. vials

20 mg. per cc.
Each cc. contains:

Medrol (methylprednisolone) acetate	20 mg.
Polyethylene glycol 4000	29.6 mg.
Sodium chloride	8.9 mg.
Myristyl-gamma-picolinium chloride	0.19 mg.
Water for injection	q.s.

Supplied: 5 cc. vials

1. Norcross, B. M., and Winter, J. A.: Methylprednisolone acetate: a single preparation suitable for both intra-articular and systemic use, New York J. Med. *61*:552 (Feb. 15) 1961.

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REFERENCES: 1. Lorber, S. H., and Shay, H.: Gastroenterology *28*:274, 1955. 2. Hock, C. W.: J. M. A. Georgia *40*:22, 1951. 3. Chamberlin, D. T.: Gastroenterology *17*:224, 1955. 4. Steves, M. F.: Ohio State M. J. *48*:615, 1952. 5. Derome, L.: Canad. M. A. J. *69*:532, 1953. 6. Pakula, S. F.: Postgrad. Med. *11*:123, 1952. 7. Guerrero, R. M., Cancio, R., and Songco, R.: Phil. J. Pediat. *2*:30, 1953. 8. Hock, C. W.: J. M. A. Georgia *43*:124, 1954. 9. Hufford, A. R.: Am. J. Digest. Dis. *19*:257, 1952. 10. Brown, D. W., and Guilbert, G. D.: Am. J. Ophth. *36*:1735, 1953. 11. Cholst, M., Goodstein, S., Berens, C., and Cinotti, A.: J.A.M.A. *166*:1276, 1958. 12. Brown, B. B., Thompson, C. R. Klahm, G. R., and Werner, H. W.: J. Am. Pharm. A. (Sc. Edit.) *39*:305, 1950. 13. Hufford, A. R.: J. Michigan M. Soc. *49*:1308, 1950. 14. McHardy, G. G., Browne, D. C., Marek, F. H., McHardy, R., and Ward, S.: J.A.M.A. *147*:1620, 1951. 15. Esses, E., Magee, D. F. and Ivy, A. C.: Gastroenterology *21*:574, 1952. 16. Northrup, D. W., Stickney, J. C., and Van Liere, E. J.: Am. J. Physiol. *171*:513, 1952.

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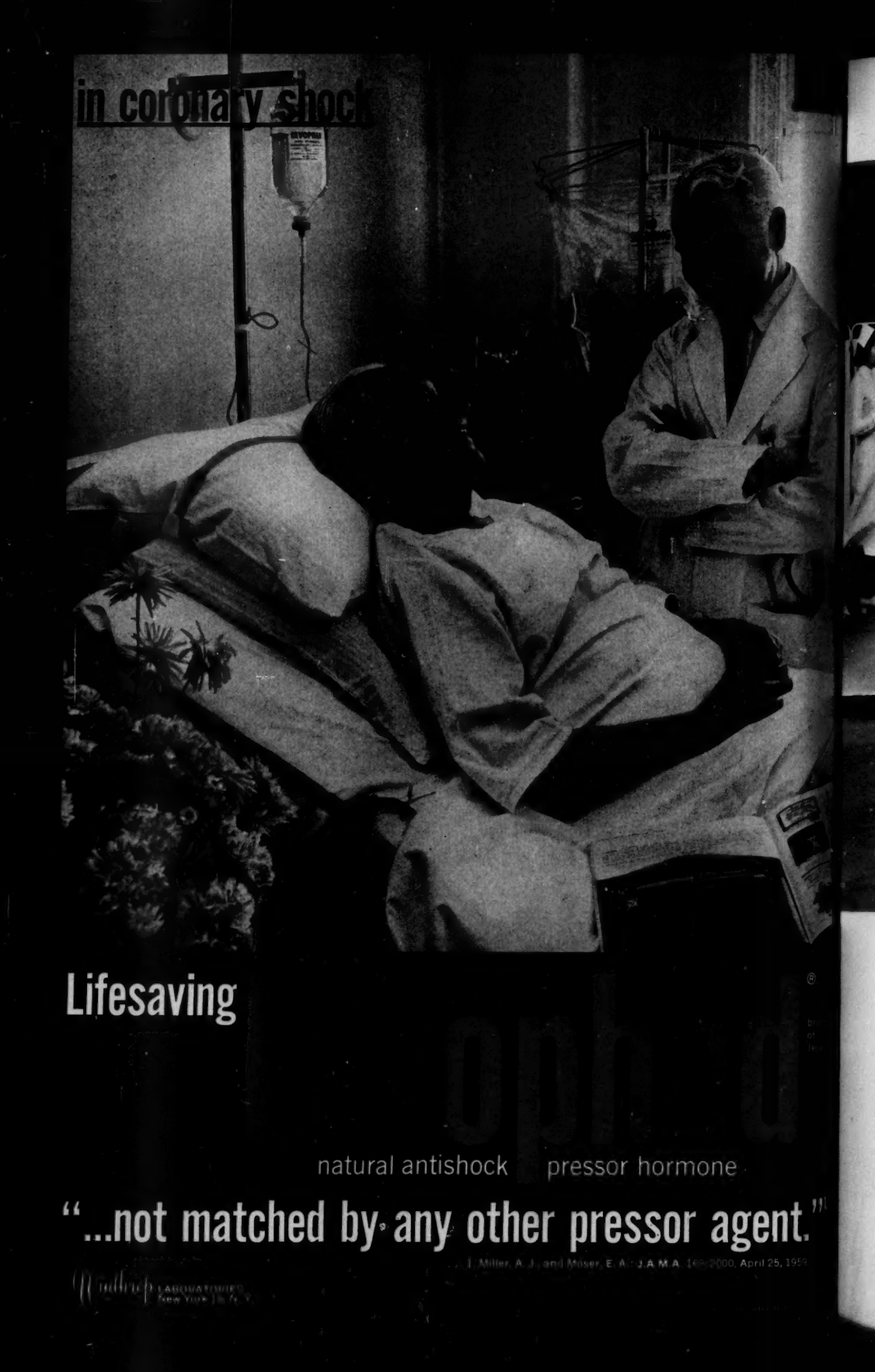
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17. Lorber, S. H., and Shay, H.: Fed. Proc. *12*:90, 1953. 18. Johnston, R. I.: J. Indiana M. A. *46*:869, 1953. 19. Marien, B., Webster, D. R., and Tidmarsh, C. J.: Gastroenterology *24*:200, 1953. 20. Hardin, J. H., Levy, J. S., and Seager, L.: South. M. J. *47*:1190, 1954. 21. Sleisenger, M. H., Eisenbud, M., and Almy, T. P.: Gastroenterology *27*:829, 1954. 22. Weiss, S.: Am. J. Gastroenterology *23*:69 (Editorial) 1955. 23. Illingworth, R. S.: Lancet *2*:1119, 1959. 24. McHardy, G. G., and Browne, D. C.: South. M. J. *45*:1139, 1952. 25. Miller, B. N.: J. South Carolina, M. A. *48*:1, 1952.

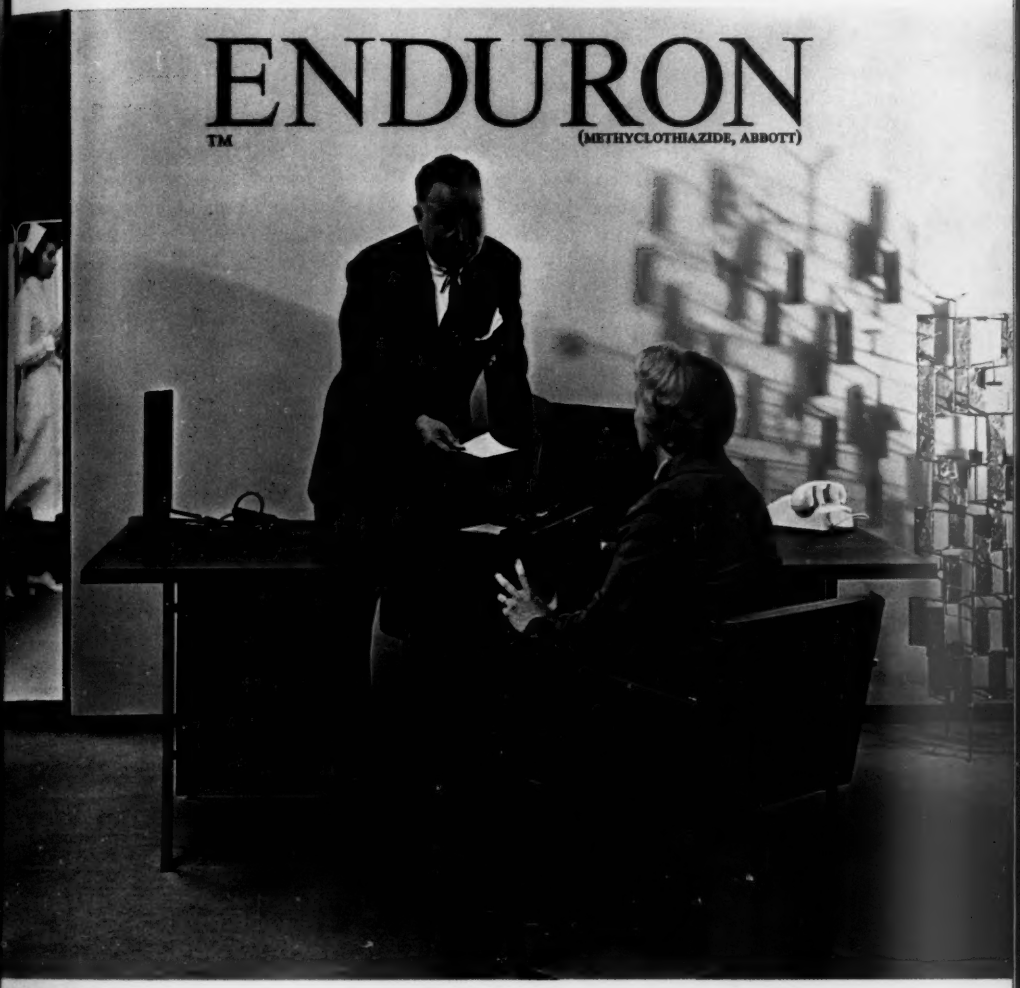
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J. Miller, A. J., and Moser, E. A.: J.A.M.A. 160:2000, April 25, 1959
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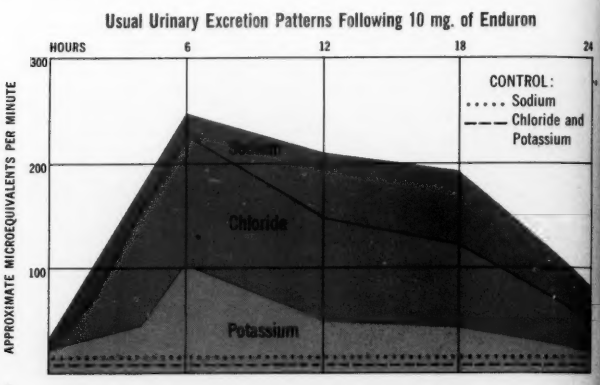
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1. Ford, R. V., Current Therap. Res., 2:422-430, Sept., 1960.
2. Bryant, J. M., et al., Current Therap. Res., 3:1-4, Jan., 1961.

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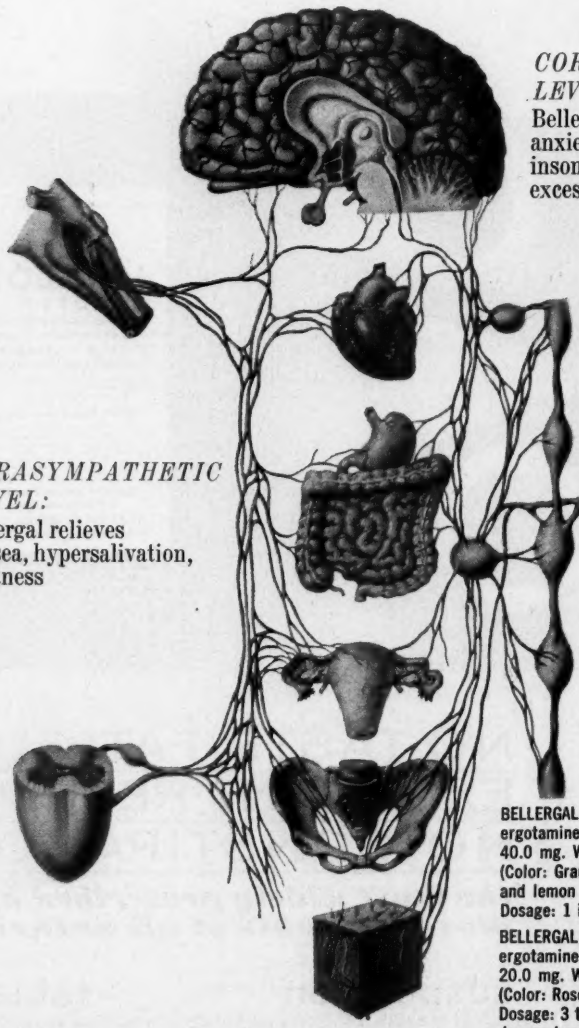
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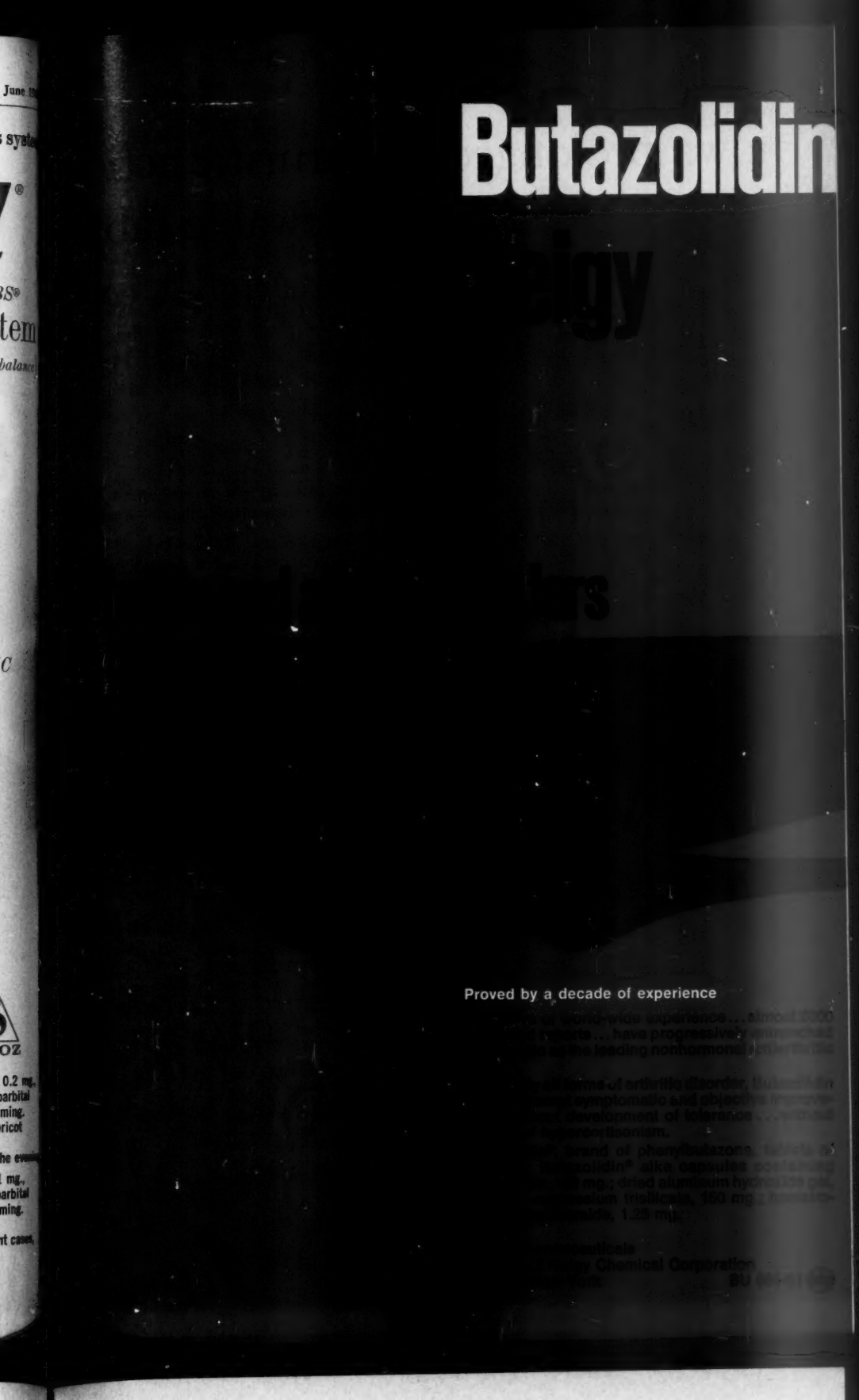
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side effects: Drowsiness has been observed in a small percentage of patients. Dizziness, nausea, headache, and dryness of mucous membranes have been reported infrequently.

cautions: If drowsiness occurs after administration of Tacaryl Chewable Tablets or Tacaryl Hydrochloride, the patient should not drive a motor vehicle or operate dangerous machinery. Since Tacaryl Chewable Tablets or Tacaryl Hydrochloride may display potentiating properties, it should be used with caution for patients receiving alcohol, analgesics or sedatives (particularly barbiturates). Because of reports that phenothiazine derivatives occasionally cause side reactions such as agranulocytosis, jaundice and orthostatic hypotension, the physician should be alert to their possible occurrence...though no such reactions have been observed with Tacaryl Chewable Tablets or Tacaryl Hydrochloride.

supplied: Pink tablets, 3.6 mg., bottles of 100.

references: (1) Lish, P. M.; Albert, J. R.; Peters, E. L., and Allen, L. E.: Arch. internat. pharmacodyn. *129*:77-107 (Dec.) 1960. (2) Howell, C. M., Jr.: North Carolina M. J. *21*:194-195 (May) 1960. (3) Clinical Research Division, Mead Johnson & Company. (4) Wahner, H. W., and Peters, G. A.: Proc. Staff Meet. Mayo Clin. *35*:161-169 (March 30) 1960. (5) Crepea, S. B.: J. Allergy *31*:283-285 (May-June) 1960. (6) Crawford, L. V., and Grogan, F. T.: J. Tennessee M. A. *53*:307-310 (July) 1960. (7) Spoto, A. P., Jr., and Sieker, H. O.: Ann. Allergy *18*:761-764 (July) 1960. (8) Arbesman, C. E., and Ehrenreich, R.: New York J. Med. *61*:219-229 (Jan. 15) 1961.

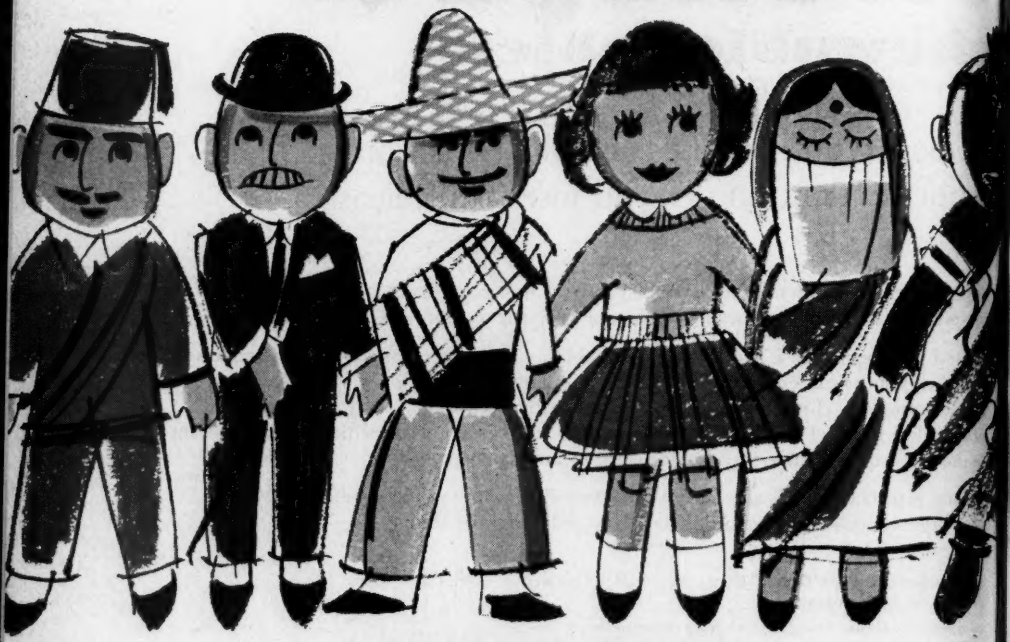
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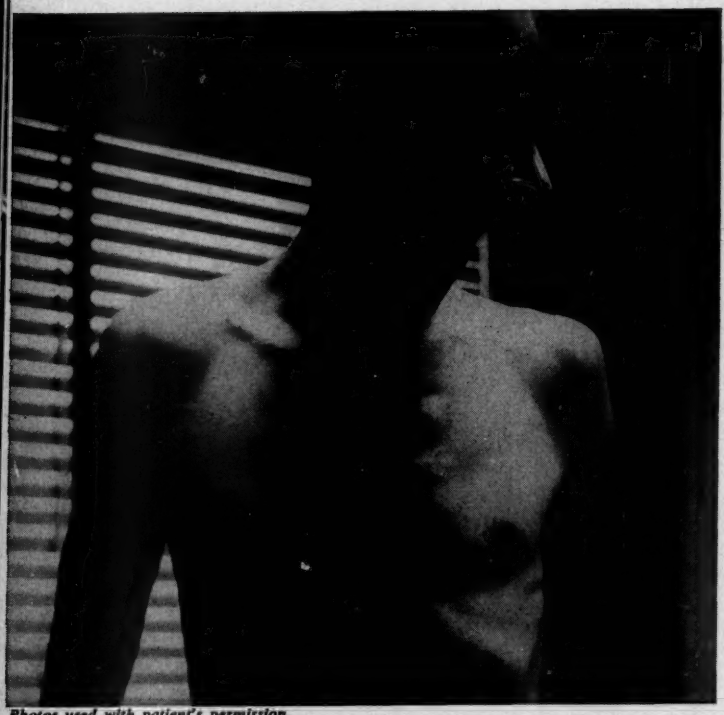
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Dianabol spares patients the i
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And because Dianabol is lo
cost, it is particularly suitable f
aged or chronically ill patient
may require long-term ana
therapy.

Supplied: *Tablets*, 5 mg. (
scored); bottles of 100.

Complete information on requ

Dianabo

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converts protein to working weight in wast or debilitated patients

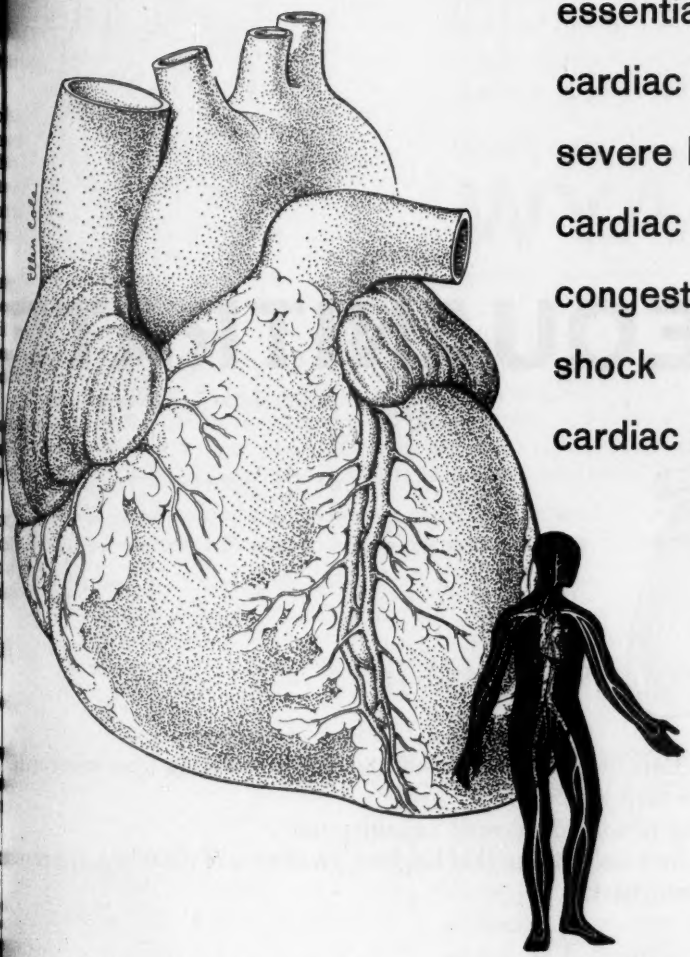
For complete information about D
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Reference or write
CIBA, Summit, N. J. 2/2829MK-2

dependable

WYETH cardiovascular agents

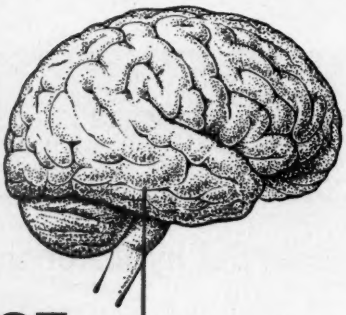
for use in . . .

angina pectoris
coronary insufficiency
essential hypertension
cardiac emergencies
severe hypotension
cardiac edema
congestive heart failure
shock
cardiac arrhythmias



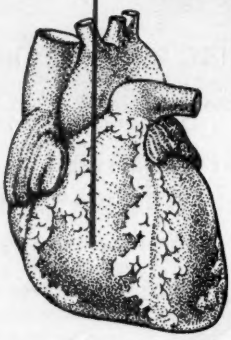
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most angina patients are "heart conscious"



EASE HEART AND MIND WITH EQUANITRATE

meprobamate and pentaerythritol tetranitrate, Wy



In patients with angina pectoris, with coronary insufficiency, or recovering from myocardi infarction, EQUANITRATE can help you

- prevent pain by providing prolonged coronary vasodilatation
- control apprehension, anxiety and tension that heighten awareness of disabling symptom
- reduce dependence on nitroglycerin
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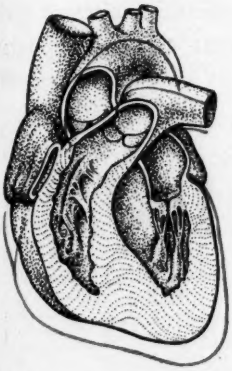
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2. *Shapiro, S.: Angiology* 10:126 (April) 1959. 3. *Friedlander, H.*
Am. J. Cardiol. 1:395 (March) 1958. 4. *Waldman, S., and Pelner, L*
Am. Pract. & Digest Treat. 8:1075 (July) 1957.

Although infrequent, adverse reactions to many modern drugs may occ
For further information on limitations, administration and prescribing
EQUANITRATE, *see descriptive literature or current Direction Circul*
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in SHOCK

and cardiac arrhythmias



WYAMINE helps reverse the physiological response to the shock state. It increases blood flow to vital organs by stimulating myocardial contraction with minimal peripheral constriction.[1] It has a unique antiarrhythmic effect; is valuable in shock of myocardial infarction,[2] hypotension of severe illness,[3] cardiac arrhythmias,[4] hypotension attending anesthesia.[5]

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WYAMINE®

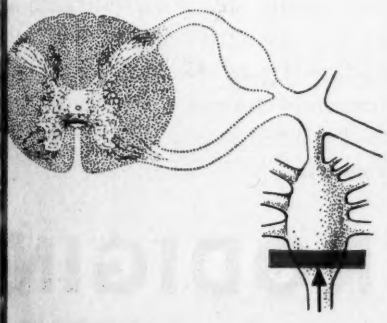
Mephentermine Sulfate, Wyeth SULFATE

References: 1. Welch, G.H., et al.: Am. J. Med. 24:871 (June) 1958. 2. Bernstein, A., et al.: Circulation 16:860 (Nov.) 1957. 3. Winsor, T.: J.A.M.A. 169:1742 (April 11) 1959. 4. Wilson, M., et al.: Am. J. M. Sc. 236:300 (Sept.) 1958. 5. Lynch, P.R., et al.: Anesthesiology 16:632 (July) 1955. 6. Borhani, N.O.: Ann. Int. Med. 51:983 (Nov.) 1959. 7. Dunsmore, R.A., et al.: Am. J. M. Sc. 236:483 (Oct.) 1958. 8. Duane, G.W., et al.: Am. Pract. & Digest Treat. 11:701 (Aug.) 1960. 9. Janney, J.G., Jr., et al.: Am. J. Cardiology 4:745 (Dec.) 1959.

Although infrequent, adverse reactions to many modern drugs may occur. For further information on administration, limitations and prescribing of OSTENSIN and WYAMINE, see descriptive literature or current Direction Circulars.

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in DIASTOLIC hypertension



OSTENSIN is an effective antihypertensive. It produces prompt, prolonged sympathetic blockade with some by-effects milder than with other ganglionic blockers.[6,7] *In conjunction with oral diuretics,[8,9] such as chlorothiazide,* OSTENSIN permits reduced dosages with resultant reduction in side-effects and excellent blood pressure response.

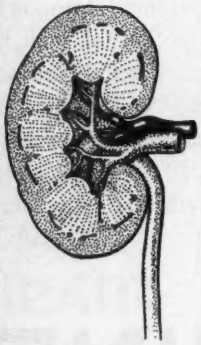
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OSTENSIN®

Trimethidinium Methosulfate, Wyeth

for prompt, positive diuresis

in cardiac edem



Parenteral THIOMERIN produces rapid, predictable, and smoo fluid loss in severe edematous states[1-3] such as cardiac ede (peripheral or pulmonary), nephrotic edema, ascites of liver di ease. Virtual freedom from local irritant actions commends u of THIOMERIN subcutaneously[4] as well as I.M. or I.V. Systemic a cardiac toxicity are extremely low.

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Mercaptomerin Sodium, Wyeth

References: 1. Modell, W. in Modell, W.: Drugs of Choice, 1958-1959, The C. V. Mosby Co., St. Louis, 1958, p. 2. Burch, G.E.: J.A.M.A. 157:1073 (March 26) 1955. 3. Brimi, R.J.: Journal-Lancet 70:298 (Aug.) 1950. 4. A.M. Council on Drugs: New and Nonofficial Drugs, J. B. Lippincott Co., Phila., 1959, p. 599. 5. Friedman, M.: Mod Concepts of Cardiovascular Disease (The American Heart Assoc.) 25:311 (Feb.) 1956. 6. Gold, H., et al.: J. Pharm. & Exper. Therap. 109:45 (Sept.) 1953.

Although infrequent, adverse reactions to many modern drugs may occur. For further information on administration, limitations and prescribing of THIOMERIN and PURODIGIN, see descriptive literature or current Direction Circulars.

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for steady digitalization

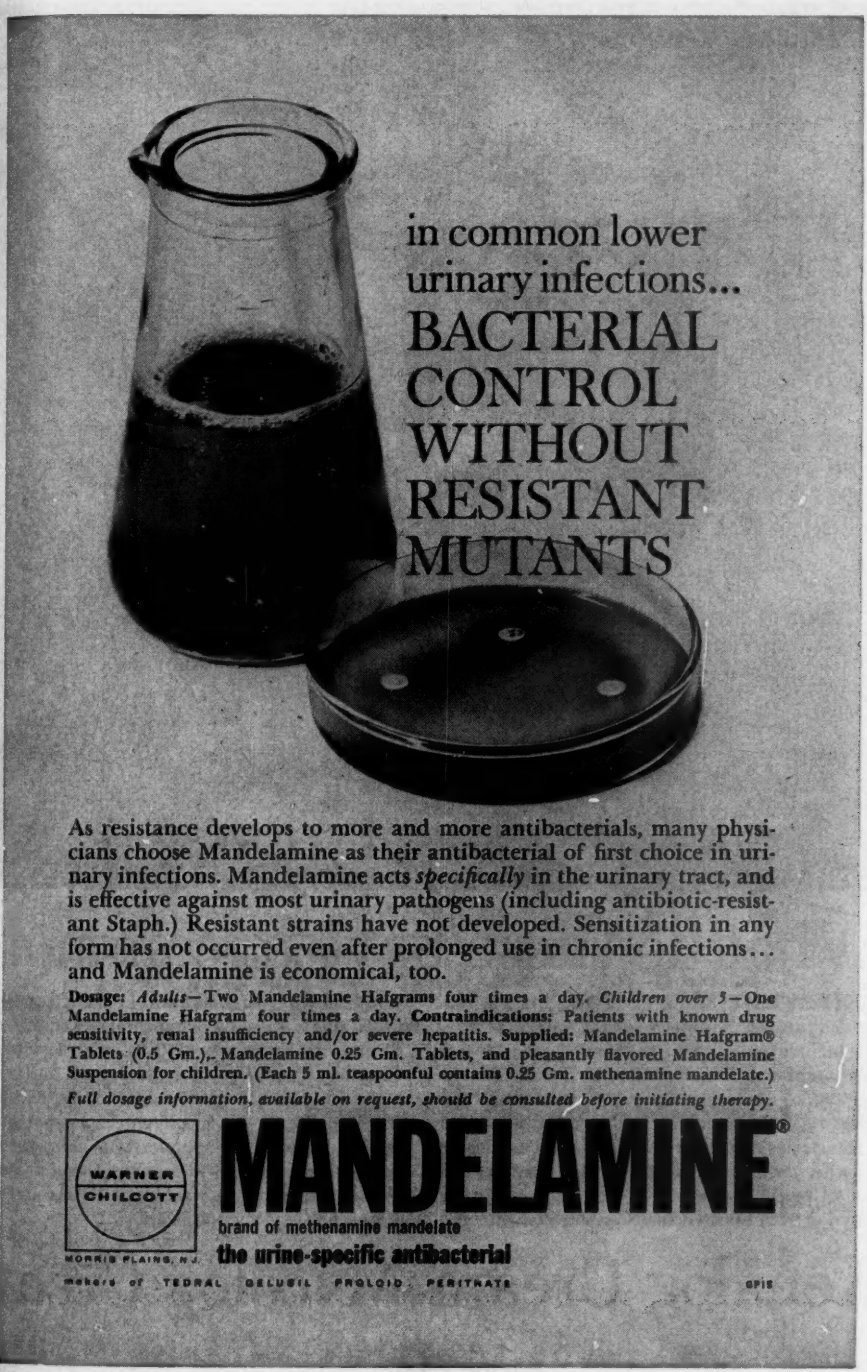
in congestive heart failur

Uniformly potent, dependably stable, and completely absorbed[5] oral administration, PURODIGIN permits steady digitalization cording to the patient's needs. The physician's ability to vary t cardiotonic dose at will helps minimize the hazards of si effects. Slow excretion[6] of PURODIGIN assures maintenance on single daily dose. In severe decompensation, therapy may initiated with intravenous PURODIGIN.



PURODIGIN

Crystalline Digitoxin, Wyet



As resistance develops to more and more antibacterials, many physicians choose Mandelamine as their antibacterial of first choice in urinary infections. Mandelamine acts *specifically* in the urinary tract, and is effective against most urinary pathogens (including antibiotic-resistant Staph.) Resistant strains have not developed. Sensitization in any form has not occurred even after prolonged use in chronic infections... and Mandelamine is economical, too.

Dosage: *Adults*—Two Mandelamine Hafgrams four times a day. *Children over 5*—One Mandelamine Hafgram four times a day. **Contraindications:** Patients with known drug sensitivity, renal insufficiency and/or severe hepatitis. **Supplied:** Mandelamine Hafgram® Tablets (0.5 Gm.), Mandelamine 0.25 Gm. Tablets, and pleasantly flavored Mandelamine Suspension for children. (Each 5 ml. teaspoonful contains 0.25 Gm. methenamine mandelate.)

Full dosage information, available on request, should be consulted before initiating therapy.

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MORRIS PLAINS, N.J.

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brand of methenamine mandelate

the urine-specific antibacterial

makers of TEDRAL DELUSIL PROLOID PERITRATE 9F1S



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SUMMERTIME SKIN DISTRESS is the factor that unites the objects here. Common offenders include poison ivy, oak and sumac; insect bites, sunburn. *Kenalog* (Squibb Triamcinolone Acetonide) topical therapy brings to these and other related warm weather dermatitis a rapid – sometimes dramatic – involution of the lesion ... with prompt relief of itching, burning and the allergic aspect. *Kenalog-S*, combining Kenalog with Spectrocin (Squibb Neomycin and Gramicidin), affords marked antibacterial protection. *Mycolog*, containing Kenalog and Spectrocin, is also formulated with Mycostatin (Squibb Nystatin) – the preferred antifungal agent in treating cutaneous candidiasis ... And *Kenalog Spray* – in a convenient aerosol unit – is well suited for summertime skin distress, particularly in hard-to-reach problem areas. For full information, see your Squibb Product Reference or Product Brief.

Kenalog Cream Mycolog Cream

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MEDICAL NEWS

Meetings

Aug. 27–Sept. 1	American Congress of Physical Medicine and Rehabilitation, Sheraton-Cleveland Hotel, Cleveland. Dorothea C. Augustin, 30 N. Michigan Ave., Chicago 2, Executive Secretary.
Sept. 27–29	American Association of Medical Clinics, Barbizon Plaza Hotel, New York. Dr. Joseph B. Davis, Clinic, 131 N. Washington St., Marion, Ind., Secretary-Treasurer.
Oct. 1–7	College of American Pathologists, Olympic Hotel, Seattle. Dr. Arthur H. Dearing, Prudential Plaza, Suite 2115, Chicago, Executive Director.
Oct. 22–25	American College of Gastroenterology, Hotel Cleveland, Cleveland. Mr. Daniel Weiss, 33 W. 60th St., New York 23, Executive Director.
Nov. 5–8	Association of Military Surgeons (68th Annual Convention), Mayflower Hotel, Washington, D. C. Rear Adm. Richard A. Kern, MC, USNR, Ret., 1726 Eye St., N. W., Washington 6, D. C., President.
Nov. 9–11	Gerontological Society, Inc., Penn-Sheraton Hotel, Pittsburgh, Pa. Gerontological Society, Inc., 660 South Kingshighway Blvd., St. Louis 10, Missouri.

International and Foreign Meetings—1961

July 2–9	First International Congress of Preventive and Rural Medicine (Congrès International de Prévention et Médecine Agricole), Tours, France. Prof. Vacher, c/o Ecole de Médecine, Tours (Indre-et-Loire), France, Secretary-General.
July 10–14	Fourth International Diabetes Federation Congress, Geneva, Switzerland. Dr. B. Rillet, 4, Boul. des Tranchées, Geneva, Switzerland, Secretary-General.
July 16–21	Fourth International Conference on Medical Electronics —Fourteenth Annual Conference on Electrical Techniques in Medicine and Biology, Waldorf-Astoria Hotel, New York City. The Institute of Radio Engineers, Inc., 1 E. 79th St., New York 21, N. Y.
Aug. 14–25	Israel Medical Association, World Assembly of the, Jerusalem, Israel. Dr. Leo Schindel, 20 Metudela St., Jerusalem, Israel.
Aug. 28–Sept. 2	European Society of Haematology, Vienna. Prof. Dr. H. Fleischhacker, Kongress-Sekretariat, Wien IX, Frankgasse 8, Billrothhaus, Austria.
Oct. 15–20	Fourth International Congress of Allergology, Hotel Commodore, New York City. Dr. William B. Sherman, 60 E. 58th St., New York 22, N. Y., Chairman.

Nov. 27–29 AMERICAN SOCIETY OF HEMATOLOGY, Ambassador Hotel, Los Angeles, Calif. Dr. Louis Lowenstein, Royal Victoria Hospital, Montreal, Quebec, President.

POSTGRADUATE COURSES

MICHAEL REESE HOSPITAL AND MEDICAL CENTER, CHICAGO, ILL.

A course in electrocardiographic interpretation for graduate physicians will be given at the Michael Reese Hospital by Louis N. Katz, M.D., and Alfred Pick, M.D. (respectively Director and Associate Director of the Cardiovascular Department) and Associates. The class will meet daily from 9:00 A.M. to 5:00 P.M., July 17th through July 29th.

Further information and a copy of the lecture schedule may be obtained upon application to Miss Beverley Petzold, Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital and Medical Center, Chicago 16, Illinois.

FITZSIMONS GENERAL HOSPITAL, DENVER, COLO.

The fourteenth annual symposium on pulmonary disease will be held at Fitzsimons General Hospital, Denver, Colorado, September 25–29, 1961. This symposium is cosponsored by the American Trudeau Society, the University of Colorado School of Medicine, and Fitzsimons General Hospital. Tuition fee is $5.00.

Information concerning enrollment may be obtained from the University of Colorado Medical School or from the Program Director, Colonel Charles S. Christianson, Pulmonary Disease Service, Fitzsimons General Hospital, Denver 30, Colorado.

UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE, SEATTLE, WASH.

A course in practical psychiatry will be offered by the Hospital of the University of Washington School of Medicine, July 24–28, 1961. For further information, write the University of Washington School of Medicine, Division of Postgraduate Medical Education, Seattle 5, Wash.

NEW YORK UNIVERSITY POSTGRADUATE MEDICAL SCHOOL, NEW YORK, N. Y.

Course No. 481 in occupational medicine will be given by the New York University Postgraduate Medical School, September 8–November 10, 1961. Tuition fee is $375, field expenses, $25.

Further information can be obtained by writing the Office of the Associate Dean, New York University Post-Graduate Medical School, 550 First Avenue, New York 16, N. Y.

AMERICAN COLLEGE OF CHEST PHYSICIANS

The Council on Postgraduate Medical Education of the American College of Chest Physicians will present the following postgraduate courses during 1961:

July 24–28 CARDIOPULMONARY PROBLEMS IN CHILDREN. Brown Hotel, Denver, Colo.

Sept. 25–29	Industrial Chest Diseases. Warwick Hotel, Philadelphia.
Oct. 23–27	Clinical Cardiopulmonary Physiology. Sheraton-Chicago Hotel, Chicago.
Nov. 13–17	Recent Advances in the Diagnosis and Treatment of Heart and Lung Diseases. Park Sheraton Hotel, New York City.
Dec. 4–8	Recent Advances in Diseases of the Chest. Statler-Hilton Hotel, Los Angeles.

Tuition for each course is $75 for members of the American College of Chest Physicians and $100 for non-members. The fee includes attendance at the round table luncheon discussions. For further information write Executive Director, American College of Chest Physicians, 112 East Chestnut St., Chicago 11, Ill.

International Psychosomatic Seminars

During the winter of 1954–55, with the introduction of the World Medical Association and the American Psychiatric Association, Dr. J. L. McCartney was extended invitations to give lectures and clinics in twenty-five different ports visited by the American President Lines. A similar cruise is to be taken during the winter of 1962–63, and physicians interested in sharing their professional experience with practitioners around the world will be welcome to take part in the International Psychosomatic Seminars. The plan is to leave New York in October or November, 1962, and a teaching seminar will be held in every port visited. Ample time will be allowed for sightseeing. Reservations will have to be made well in advance, but if a sufficient number of qualified persons volunteer their services, then further Psychosomatic Seminars will be organized.

For further information write James L. McCartney, M.D., 223 Stewart Avenue, Garden City, N. Y.

Examinations and Licensure

American Board of Psychiatry and Neurology: Chicago, Oct. 9–10, 1961. Sec., David A. Boyd, Jr., 102–110 Second Ave., S. W., Rochester, Minn.

Medical Periodicals for the World Medical Association

The World Medical Association is requesting that American physicians help to provide medical periodicals and books to foreign libraries, medical groups, and hospitals. It is requested that interested physicians provide the W. M. A. with the names of the periodicals which they are willing to send regularly overseas. Wrappers addressed to a foreign physician in need of a particular publication will be furnished the donor. For further information please write: World Medical Association, U. S. Committee, Inc., 10 Columbus Circle, New York 19, N. Y.

Leukemia Research Scholarships

A program of long-term support for career investigators in leukemia research has been announced by The Leukemia Society. From five to ten Leukemia Society scholars will be selected in 1961 to receive awards ranging from $50,000 to $75,000 a year. The scholars will receive support from the society for a period of five years at salaries from $10,000 to $15,000 per year. Scholars will be nominated by the heads of medical schools and research institutes and will be chosen by the society's advisory board. Interested physicians should contact Mr. Richard Mitchell, National Director, The Leukemia Society, 405 Lexington Avenue, New York 17, N. Y.

Chest Physicians Establish Fund to Assist Cuban Members

At a meeting of the Board of Regents of the American College of Chest Physicians held in Washington, D. C., November 28, 1960, a resolution was adopted to establish a relief fund for Cuban members of the College who have been temporarily exiled from their country. The Board of Regents voted to contribute $5,000 to launch the fund, and contributions are being solicited from College members and others who are interested. The Cuban Chapter of the College was founded in 1940, and now has 74 members.

For further information, write Executive Director, the American College of Chest Physicians, 112 E. Chestnut St., Chicago 11, Ill.

Other Announcements

One-Year Advanced Training for Physicians

Oak Ridge Institute of Nuclear Studies

The Oak Ridge Institute of Nuclear Studies announces a one-year advanced training program for physicians. Activities include patient care and clinical training in uses of radioisotopes as tracers and therapeutic agents. Teaching rounds are conducted three times each week. Opportunities for participation in research are offered. Residency is approved by the American Medical Association for one-year basis credit in internal medicine.

Applicants must have completed, with distinction, an internship and at least two years' approved training in internal medicine. Salary is $5,400 annually, which is subject to social security and income tax deductions. The hospital does not have facilities for residents' room and board.

The program includes the four-week basic course in radioisotope technics offered by the Institute's Special Training Division; the usual fee for the course is waived and physicians receive their regular salary while attending the course.

Forms for making application for these programs are available from Ralph M. Kniseley, M.D., The Medical Division, Oak Ridge Institute of Nuclear Studies, Post Office Box 117, Oak Ridge, Tenn.

University of Colorado School of Medicine Announces Cochems Competition

The University of Colorado School of Medicine announces the Cochems Competition, funds for which were provided in the will of the late Mrs. Jane Nugent Cochems. A prize of $2,500 will be awarded to the author of the best paper on the

subject, "The Diagnosis, Etiology and Treatment of Thrombophlebitis." The competition is open to all physicians, and entries must be received, in triplicate, on or before October 1, 1961.

The Colorado National Bank of Denver, Trustee under the will of Jane Nugent Cochems, has requested the Dean of the University of Colorado School of Medicine to conduct the competition. The judges, appointed by him, are Dr. Michael E. DeBakey, Professor and Head of the Department of Surgery, Baylor University College of Medicine, and Dr. Sol Sherry, Professor of Medicine, Washington University School of Medicine.

Papers submitted in the competition may not be published until after the winner of the competition has been announced. At that time, the winning paper and all others may be published at the discretion of individual authors. It should be noted, however, that those involved in conducting the competition will not assume any responsibility for submitting manuscripts for publication nor for any costs incident thereto. The winning paper, if published, must carry the designation, "Awarded the Jane Nugent Cochems Prize."

Questions regarding the competition and all manuscripts should be directed to Dr. Robert J. Glaser, Vice-President for Medical Affairs and Dean of the University of Colorado School of Medicine, University of Colorado Medical Center, 4200 East Ninth Avenue, Denver 20, Colorado.

Medical Research Fellowships and Grants

The Life Insurance Medical Research Fund is now receiving applications for two types of awards to be available July 1, 1962, as follows: (1) *Until October 1, 1961,* for postdoctoral research fellowships. Candidates may apply for support in any field of the medical sciences. Preference is given to those who wish to work on fundamental problems, especially those related to cardiovascular function or disease. Minimum stipend $4,500 with allowances for dependents and necessary travel; (2) *Until November 1, 1961,* for grants to institutions in aid of research on cardiovascular problems. Support is available for physiological, biochemical, and other basic work broadly related to cardiovascular problems as well as for clinical research in this field. Further information and application forms may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 1030 East Lancaster Avenue, Rosemont, Penna.

Fourth Annual MMM Awards for Medical Writing

The Editors of *Modern Medical Monographs* announce the 1961 competition for unpublished manuscripts on clinical subjects in the field of internal medicine. The purpose of these annual awards, which are known as the *Modern Medical Monographs* Awards, is to stimulate young physicians to communicate their work in the classical form of the monograph and to achieve high standards of medical writing.

The first prize is $500. In addition, the authors of other top-ranking manuscripts which are found suitable will be offered a contract for publication of their work as a book in the series *Modern Medical Monographs* under standard royalty arrangements. The generosity and cooperation of Dr. Henry M. Stratton, President, Grune & Stratton, Inc., publishers of the series, have made these awards possible.

The entries will be judged for style and clarity of expression by a committee of the American Medical Writers' Association, and for clinical interest and scientific value by the Editors and Advisory Board of *Modern Medical Monograps.*

Following are the rules of the competition:

1. The author must be a graduate physician, less than 40 years of age.

2. Manuscripts (including illustrations, if any) should be submitted in duplicate (original and one copy) by registered mail, postmarked no later than December 1, 1961, to Irving S. Wright, M.D., 450 East 69th Street, New York 21, N. Y.

3. The manuscript, including the bibliography, must consist of not less than 130, or more than 200, double-spaced typewritten pages with one-inch margins, and not more than 30 illustrations (pictorial charts, drawings, diagrams, or photographs).

4. Fishbein's book, *Medical Writing* (3rd Ed.), should be followed in preparation of the manuscript, use of abbreviations, etc., and bibliographic form.

For matched tubular diuresis



IN BOTH PROXIMAL AND DISTAL SEGMENTS

HYDROCHLOROTHIAZIDE
acts mainly in the proximal segments of the renal tubules.

ALDACTONE® (spironolactone)
acts mainly in the distal segments of the renal tubules.

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ALDACTAZIDE now offers physicians the only therapeutic preparation to provide positive diuretic activity in both the *proximal* and the *distal* segments of the renal tubules.

Hydrochlorothiazide exerts a well-known, vigorous diuretic action in the *proximal* segment of the renal tubules. The Aldactone component of Aldactazide specifically blocks the sodium-retaining and potassium-excreting effect of aldosterone in the *distal* segment.

This combined control provides true multiple diuretic effects for optimal relief of edema and ascites in patients requiring prompt, maximal control, and in those whose edema and ascites are resistant to single diuretics. Further, the potassium-saving activity in Aldactazide largely or wholly offsets the danger of potassium loss which thiazide diuretics induce.

The usual *adult* dose of Aldactazide is one tablet four times daily, although dosage may range from one to eight tablets daily.

Aldactazide is supplied as compression-coated white tablets, each tablet containing 75 mg. of Aldactone (brand of spironolactone) and 25 mg. of hydrochlorothiazide.

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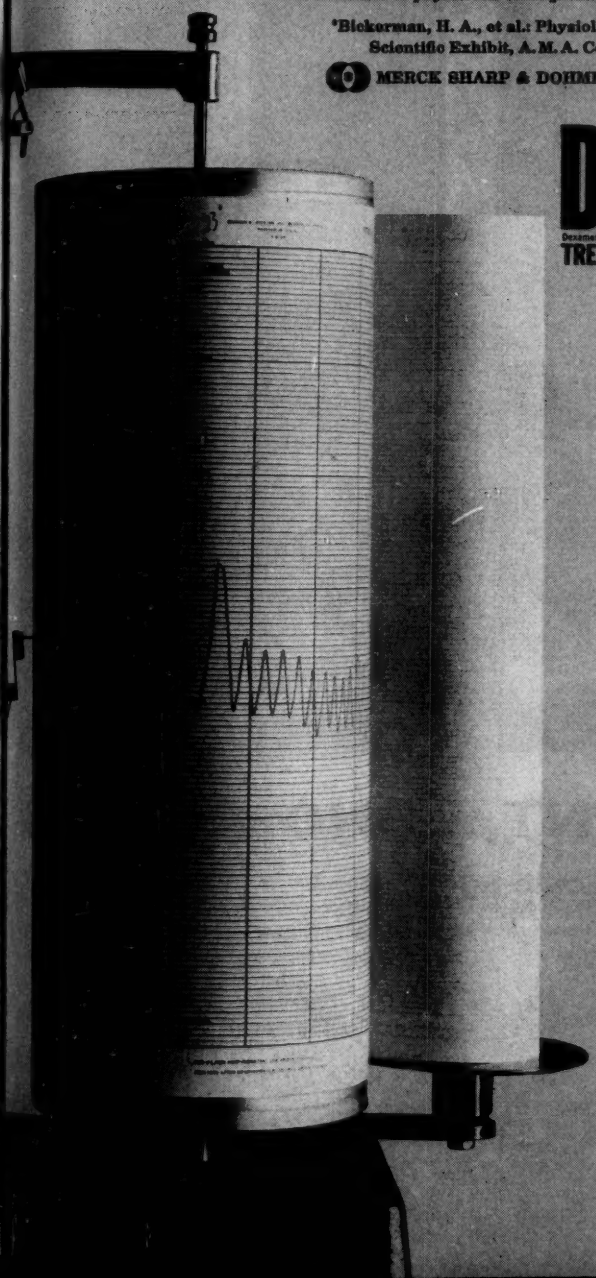
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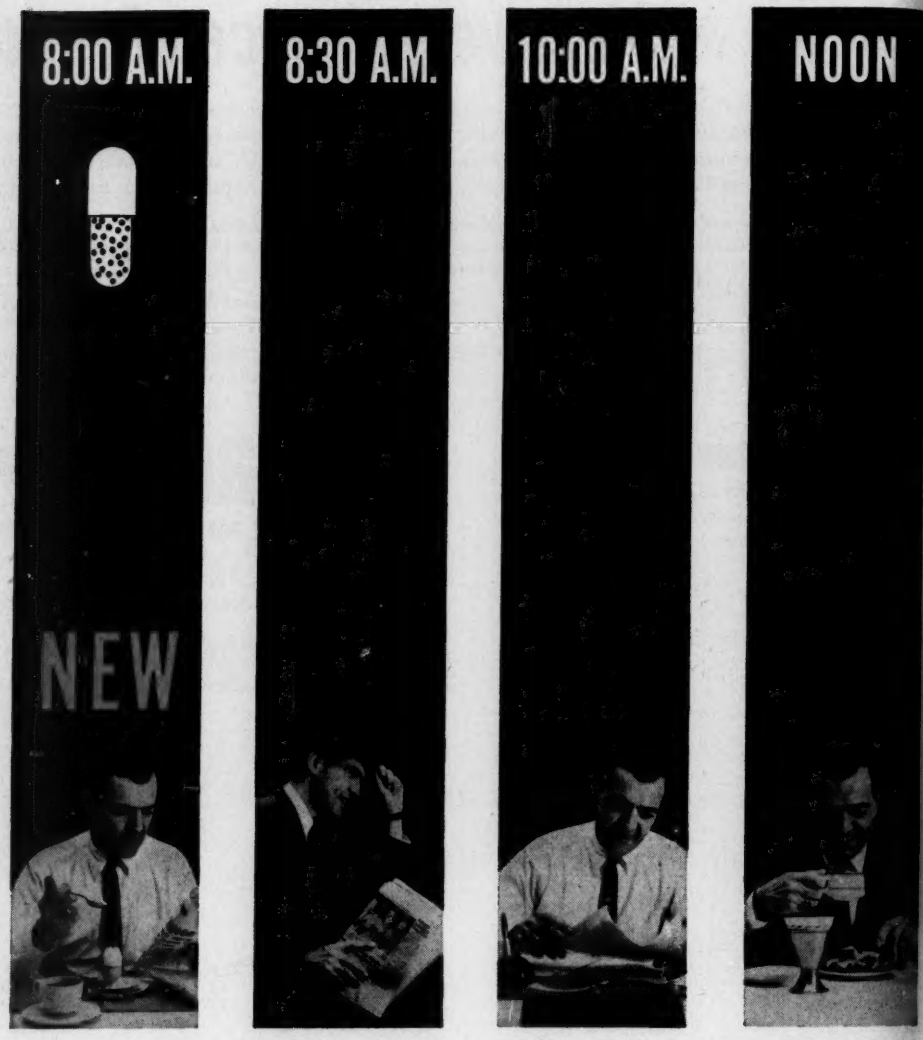
*Bickerman, H. A., et al.: Physiologic and steroid therapy in respiratory disease, Scientific Exhibit, A.M.A. Convention, Atlantic City, N. J., June 8-12, 1959.

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TUESDAY NIGHT, JUNE 27, 1961
A portrait of the family physician and his special contributions to the health of the nation

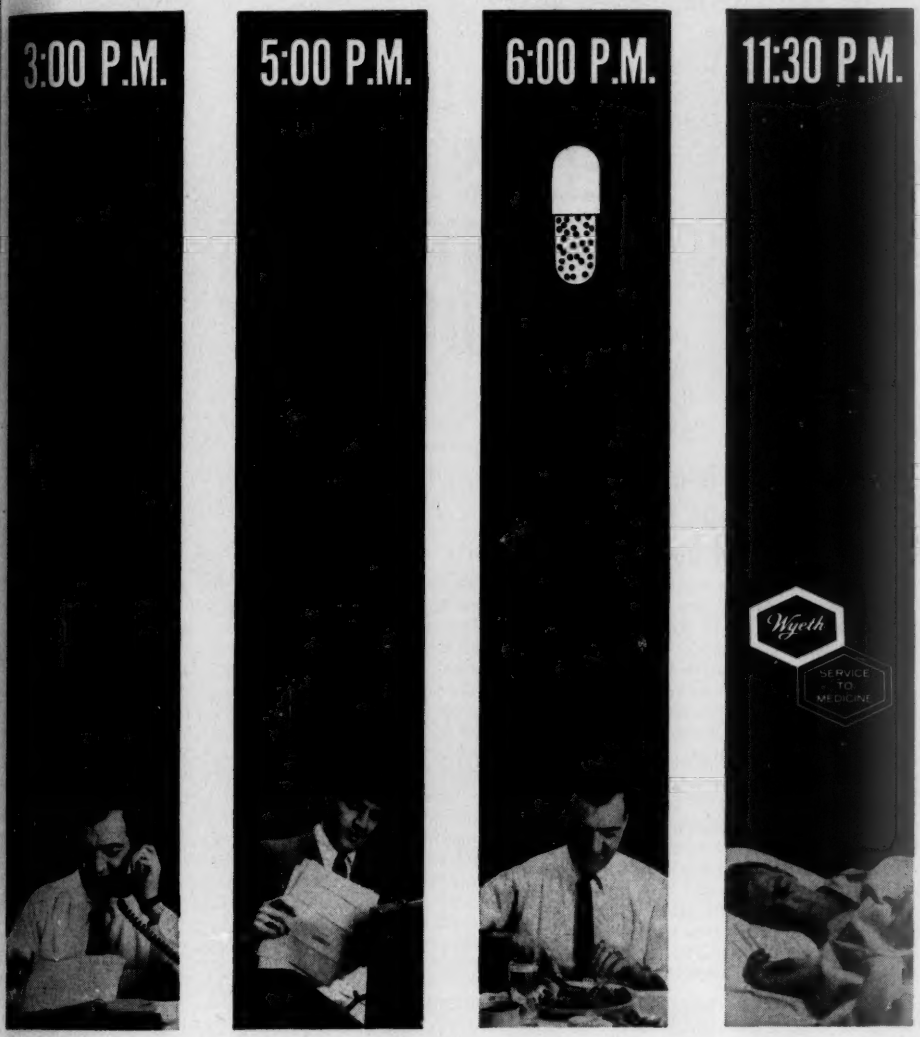


CONVENIENT, LONG-ACTING

the predictable, specific agent to
relieve anxiety and tension

EQUA

meprobamate, Wyeth



FORM OF EQUANIL

The average adult daily dose is 1 capsule twice a day although a dosage range up to 2 capsules twice a day may be required by certain patients. Supplied: 400 mg. capsules.

For further information on limitations, administration and prescribing of EQUANIL L-A, see descriptive literature or current Direction Circular. Wyeth Laboratories Philadelphia 1, Pa.

NIL® L-A

CAPSULES



in sulfa therapy..

RELEASE YOUR PATIENT FROM Q.I.D. DOSAGE

just one tablet of Midicel provides continuous, effective blood levels for 24 hours

Because many patients need take only 1 tablet daily, therapy with MIDICEL is convenient and economical. It is also advantageous since the possibility of omitted doses is reduced. Rapidly absorbed and slowly excreted, MIDICEL assures dependable bacteriostatic action in urinary tract infections, certain respiratory infections, bacillary dysenteries, as well as surgical and soft-tissue infections caused by sulfonamide-sensitive organisms. And with MIDICEL, there is little likelihood of crystalluria because of its high solubility and low dosage.

MIDICEL (sulfamethoxypyridazine, Parke-Davis), 3-sulfanilamido-6-methoxypyridazine. Tablets of 0.5 Gm.; Suspension, each cc. containing 50 mg. of sulfamethoxypyridazine as the N^1-acetyl derivative. *Indications:* Gram-negative and gram-positive infections such as urinary tract, respiratory, and soft-tissue infections and bacillary dysenteries. *Dosage:* Orally once a day until asymptomatic for 48 to 72 hours. Adults:—1 Gm. initially, followed by 0.5 Gm. daily thereafter or 1 Gm. every other day. In severe infections, not to exceed 2 Gm. the first day, then 0.5 to 1.5 Gm. daily according to weight of patient and severity of infection. Children:—30 mg. per Kg. the first day, then 15 mg. per Kg. daily. In severe infections, up to 50 mg. per Kg. initially, then 25 mg. per Kg. daily. Total dose in children, however, should not exceed lower dosage limits for adults. *Precautions:* Continue daily doses higher than 0.5 Gm. no longer than three to five days without checking for blood levels above therapeutic range. Maintain adequate fluid intake during therapy and for 48 to 72 hours afterward. Until further definitive information is available, MIDICEL, in common with all sulfonamides, is contraindicated in the premature and newborn infant. Contraindicated in patients with a history of sulfa sensitivity. MIDICEL is not recommended for meningococcal infections. *Side Effects:* Anorexia and lassitude may occur as may reactions such as drug fever, rash, and headache, all of which are indications for discontinuing the drug. Leukopenia has been reported. Periodic blood counts are advised. Patients with impaired renal function should be followed closely since excessive accumulation may occur. AVAILABLE: Quarter-scored tablets of 0.5 Gm., bottles of 24, 100, and 1,000.

46643

Midicel®

(sulfamethoxypyridazine, Parke-Davis)

and for children... Midicel Acetyl Suspension (N^1 acetyl sulfamethoxypyridazine, Parke-Davis) • delicious butterscotch flavor • only one dose a day

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for controlled therapeutic nutrition

during hospitalization and throughout convalescence

SUSTAGEN®

Complete therapeutic nutriment

to supply all or part of the patient's nutritional requirements

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For the undernourished geriatric patient admitted to the hospital, Sustagen supplies a therapeutic diet of carefully controlled, essential nutrients to promote good nutrition and hasten convalescence.[1,2] Ideal when tube feeding is necessary,[1] Sustagen is palatable to patients as a beverage.[2]

in the home...

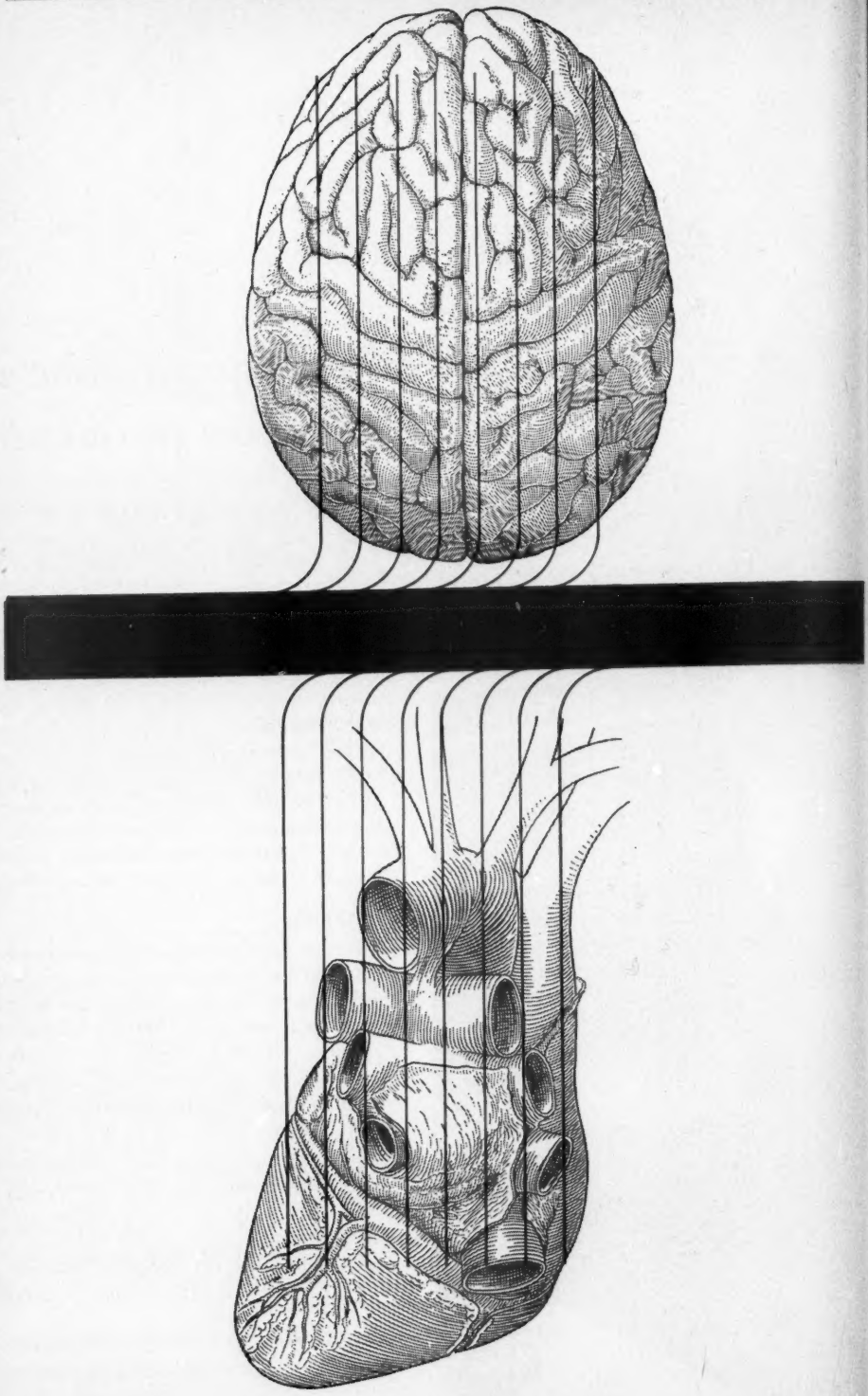
During his convalescence at home, the older patient who continues to receive Sustagen is more likely to hold or increase his nutritional gains. Each glassful you specify adds 390 calories to his diet, including 23.5 Gm. protein, 3.5 Gm. fat, and 66.5 Gm. carbohydrate – plus important quantities of all essential vitamins and minerals.

references

(1) Pareira, M. D., *et al.:* J.A.M.A. *156*:810-816 (Oct. 30) 1954.
(2) Winkelstein, A.: Am. J. Gastroenterol. *27*:45-52 (Jan.) 1957.

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Symbol of service in medicine 298811



To lift depression

Marplan covers the broad range of depressive states, including seemingly mild but progressively deteriorating conditions, many "masked" depressions, suicidal ideation, as well as depressions necessitating hospitalization. It increases accessibility of the withdrawn or regressed individual, improving rapport between physician and patient.

Where prior therapy has failed, Marplan often produces dramatic results. Prompt social recovery, *e.g.*, was achieved with Marplan in a "severe, chronic, obsessive-compulsive neurotic illness" of 20 years' duration, disabling the patient for 12 years; previous treatment had included tranquilizers and ECT.[6]

A single agent, with two distinct primary effects, for two important clinical indications

Marplan

a happy balance of potency/safety

To control pain in "difficult" cases of angina pectoris

Marplan prevents anginal pain,[1-3] increases exercise tolerance[2,4,5] and reduces nitroglycerin requirements.[2,3] It is designed for use on a continuous schedule by patients with moderately severe to intractable angina pectoris.

Marplan improves the mental climate: Not only could anginal patients placed on Marplan "... do more than formerly ..."[4] but they also felt better, were more alert, more cheerful.[2,4] The loss of pain as a warning signal against undue exertion may be balanced by close patient supervision, strict guidance, and by maintaining all restrictions of activity in force prior to Marplan therapy.

Marplan has been shown to be considerably more potent than certain other amine oxidase regulators. One might expect such potency to be associated clinically with increased side effects. Actually, Marplan strikes a happy balance of potency and safety, exhibiting a marked decrease in certain of the hydrazine side reactions; there have been no reports of hepatitis attributable to Marplan. Nevertheless, all precautions set forth in the product literature should be strictly observed.

Consult literature and dosage instructions, available on request, before prescribing.

Selected bibliography from 38 published papers: 1. W. Hollander and R. W. Wilkins, in J. H. Moyer, Ed., Hypertension, Philadelphia, W. B. Saunders Co., 1959, p. 399. 2. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 3. N. Bloom, *Virginia M. Month.*, 87:23, 1960. 4. C. C. Griffith, *Clin. Med.*, 6:1555, 1959. 5. C. C. Griffith, *Dis. Nerv. System*, 21:(Suppl.), 101, 1960. 6. L. Alexander and S. R. Lipsett, *Dis. Nerv. System*, 20:(Suppl.), 26, 1959.

MARPLAN® — 1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine

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Division of Hoffmann-La Roche Inc.

Hyland

NEW...

LE-test™

a rapid slide screening test for

Systemic Lupus Erythematosus

This simple test has demonstrated a high degree of specificity for the antinuclear factors associated with systemic lupus erythematosus (SLE). Latex-Nucleoprotein Reagent (prepared from polystyrene latex and desoxyribonucleoprotein) reacts clearly and speedily with one drop of serum from patients with active SLE. It does not react with serum from patients with classic rheumatoid arthritis.

In addition to helping differentiate SLE from other collagen diseases, LE-TEST is particularly useful as an aid in ruling out SLE as the cause of unexplained or non-specific signs and symptoms.

LE-TEST is now available for your laboratory.

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Branch office: 160 Lockwood Ave., Yonkers, N.Y.

Other Hyland latex-fixation rapid slide screening tests: RA-TEST® for detection of rheumatoid factor in rheumatoid arthritis; GG-TEST® for detection of agammaglobulinemia; CR-TEST® for detection and quantitation of C-reactive protein; FI-TEST® for detection of hypofibrinogenemia; TA-TEST® for detection of thyroglobulin autoprecipitin associated with Hashimoto's thyroiditis; Latex-Trichina Reagent, for detection of trichinosis.

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of DIAGNOSIS and THERAPY

The new MERCK MANUAL is thoroughly in step with recent diagnostic and therapeutic developments. It offers broadened coverage with the addition of 20 new subjects. Each of its 21 main sections has been updated. As with previous editions dating back 60 years, the book's objective is to provide the medical and allied professions with a current reference so as to facilitate accurate diagnosis and promote the employment of effective treatment.

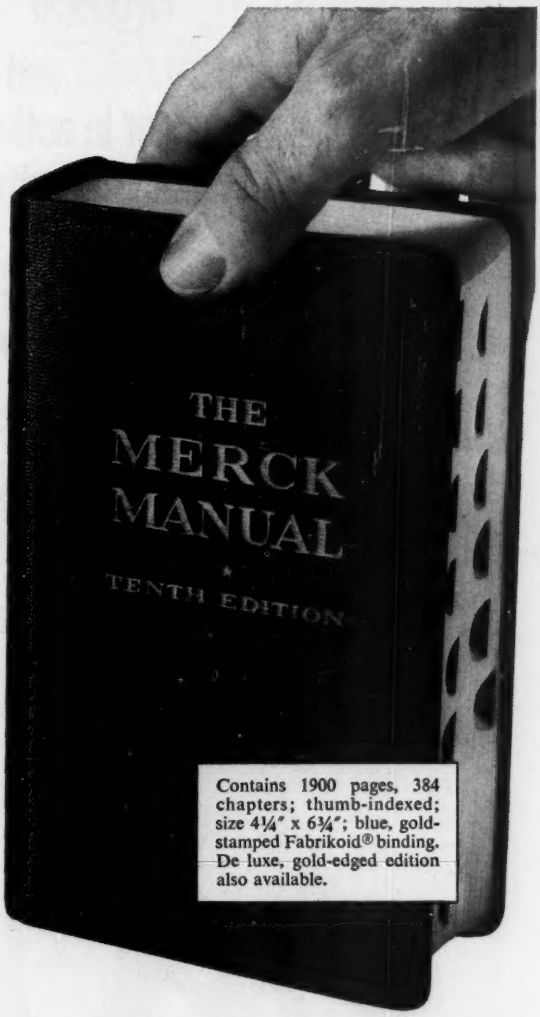
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A wide variety of disorders, not covered previously, appear in the new Tenth Edition. Disturbances in inorganic metabolism, dental and oral developmental defects, the malabsorption syndrome, group A streptococcal infections, toxoplasmosis, pulmonary granulomatoses, newly recognized viral diseases, and genetic metabolic anomalies are all included.

Other revisions deal with the care of normal newborns and preschool children; antihistamine, thrombolytic, diuretic, and psychopharmacologic therapy; the dermatitides; resuscitation methods; tubeless gastric analysis, rheumatoid arthritis tests, identification of tumor cells in body fluids, the diagnostic use of radioisotopes, and many others.

More than 100 authorities in various fields of medicine served as authors or consultants in the handbook's preparation. Several hundred prescriptions are included along with nine special therapy chapters—grouped in one section categorized according to clinical indications and mode of action.

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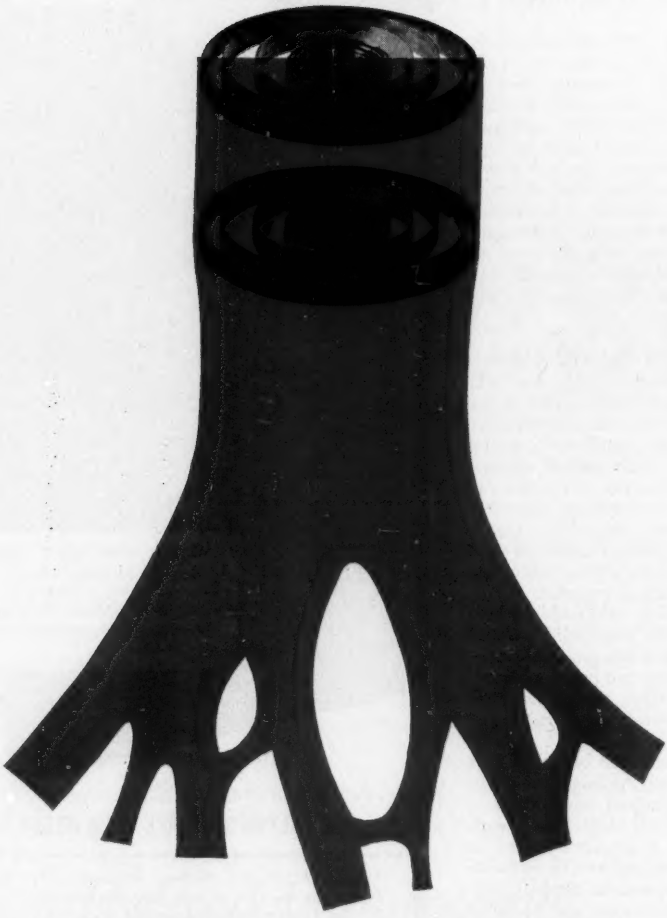
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in hypertension and edema, longer in action smoother in effect



Longer action[1] provides smooth, evenly-sustained therapeutic effect.[2] ■ Potent antihypertensive properties facilitate effective treatment of hypertension, frequently without auxiliary agents.[3] ■ Safeguards against significant potassium loss.[4] ■ Intensity of saluretic action enables liberalization of dietary salt restriction.[3] ■ Simplified dosage schedule affords economy of maintenance on just 3 doses per week.[2]

References: 1. Ford, R. V.: Current Therap. Research 2:347, 1960. 2. Fuchs, M., and others: Current Therap. Research 2:11, 1960. 3. Ford, R. V.: Connecticut Med. 24:704-707, (Nov.) 1960. 4. Ford, R. V.: Texas State J. Med. 56:343, 1960.
Detailed literature available on request.
Hygroton®, brand of chlorthalidone, is available as white, single-scored tablets of 100 mg.

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'LEUKERAN'® brand

CHLORAMBUCIL (formerly known as C. B. 1348)

FOR CHRONIC LYMPHOCYTIC LEUKEMIA

A derivative of nitrogen mustard, it has provided amelioration of follicular lymphoma, lymphocytic lymphoma with or without leukemia, and Hodgkin's disease.

Sugar-coated Tablets of 2 mg.

'MYLERAN'® brand

BUSULFAN

FOR CHRONIC MYELOCYTIC LEUKEMIA

'Myleran' has been reported to induce remissions, lasting up to two years, in chronic myelocytic leukemia. In addition to the decrease in total white cell count and selective reduction of immature myeloid cells, it usually gives, early after its administration, a rise in hemoglobin level and pronounced subjective improvement.

Tablets of 2 mg.

'PURINETHOL'® brand

MERCAPTOPURINE

FOR ACUTE LEUKEMIA AND CHRONIC MYELOCYTIC LEUKEMIA

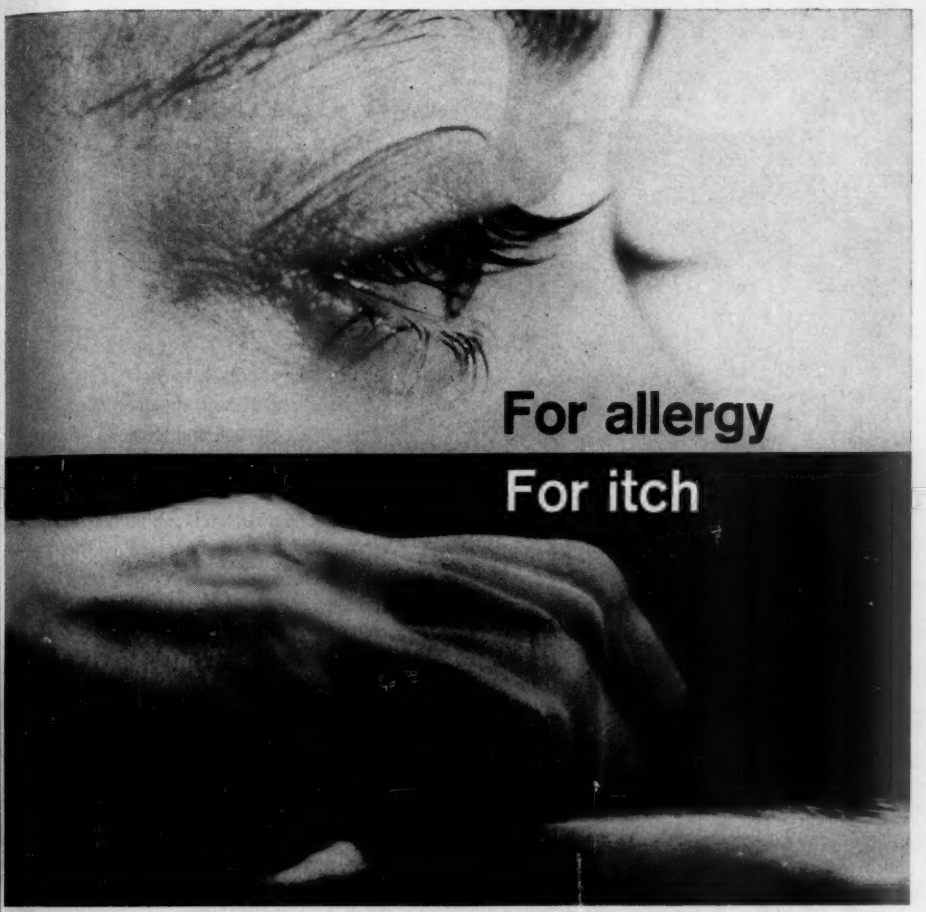
'Purinethol' provides worth-while temporary remissions, either partial or complete, in a high percentage of patients. In general, a higher proportion of children than adults with acute leukemia respond favorably.

Tablets of 50 mg.

Facilities for complete and frequent blood counts must be available for patients receiving 'Leukeran', 'Myleran' or 'Purinethol'.

Full information about these products will be sent on request.

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Everyday practice report:

Following initial clinical investigational work, Forhistal was sent to physicians throughout the country for evaluation as an antiallergic and antipruritic agent in everyday practice. Results in 6181 cases have now been analyzed. In 3419 cases in which a comparison was made, Forhistal was judged better than previous therapy in 7 out of 10 patients. Information about the investigational work done previously is being mailed to you separately and is also available on request.

SUPPLIED: *Tablets*, 1 mg. (pale orange, scored). *Lontabs*, 2.5 mg. (orange). *Syrup* (pink), containing 1 mg. Forhistal maleate per 5-ml. teaspoon. *Pediatric Drops* (pink), containing 0.5 mg. Forhistal maleate per 0.6 ml.

For complete information about Forhistal (including dosage, cautions, and side effects), see Physicians' Desk Reference or write CIBA, Summit, N.J.

FORHISTAL® maleate (dimethpyrindene maleate CIBA)
LONTABS® (long-acting tablets CIBA)

new Forhistal® rated better than previous therapy in 7 cases out of 10

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SUMMIT, NEW JERSEY

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a spreading pattern of therapeutic success

A rewarding approach to the emotional and somatic manifestations of anxiety, agitation and tension, Librium therapy is now being utilized in many different areas of general practice. Approximately 3.5 million Librium-treated cases, as well as more than 70 published reports, offer testimony to this spreading pattern of therapeutic success. They corroborate observations, gained over a span of more than three years, that Librium is pharmacologically and clinically **in a class by itself.**

Librium has been found of value in alleviating anxiety and tension associated with:

- **emotional disturbances**
- **personality disorders**
- **cardiovascular conditions**
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- **gynecologic disorders**
- **dermatologic conditions**
- **psychiatric disorders**

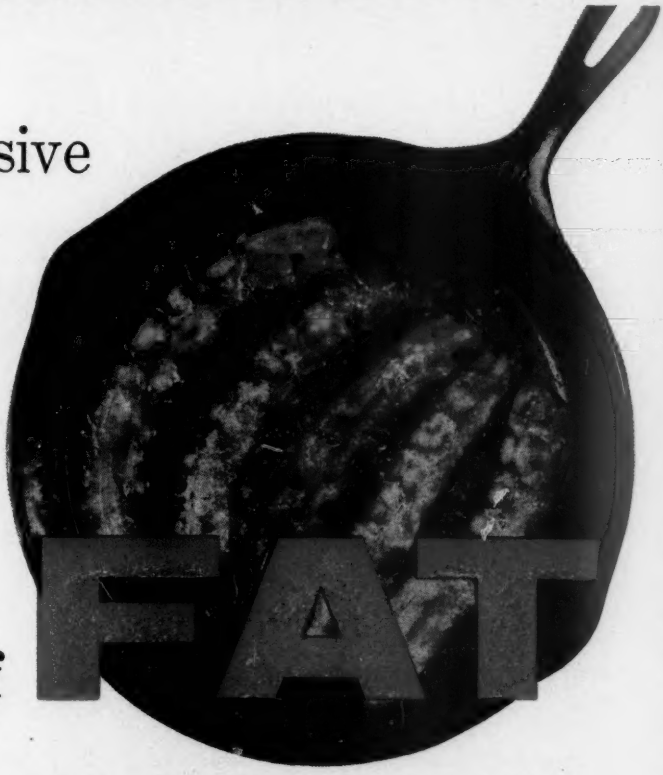
Consult literature and dosage information, available on request, before prescribing.

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THE SUCCESSOR TO THE TRANQUILIZERS

LIBRIUM® Hydrochloride—
7-chloro-2-methylamino-5-phenyl-3H-1,
4-benzodiazepine 4-oxide hydrochloride

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NEW comprehensive digestant with the *most potent* enzyme available for digestion of



—also unsurpassed potency for digestion of starch, protein and cellulose

—the *only* digestant with Lipancreatin,* proven superior to Pancreatin N.F.

—the *only* digestant with fat-splitting lipase activity 12 times as great as that of Pancreatin N.F.

When the question is digestion because of your patient's inability to handle fat, starch, protein or cellulose, you can provide dependable relief with COTAZYM-B, which contains the essential pancreatic enzymes lipase, trypsin and amylase, plus bile salts and cellulase. A daily dose of 6 COTAZYM-B tablets is sufficient to emulsify and digest 50 Gm. of dietary fat, and to digest all of the protein and starch in a typical diet (100 Gm. protein, 250 Gm. starch) and 480 mg. cellulose.

Dosage: **1 or 2 tablets with water just before each meal.**

Supply: **Bottles of 48 tablets.**

Write for samples and comprehensive literature.

NEW Cotazym®-B

Lipancreatin Bile Salts Cellulase

ORGANON INC., West Orange, New Jersey

'The Significance of Lipancreatin (Pancreatic Enzymes Concentrated 'Organon')

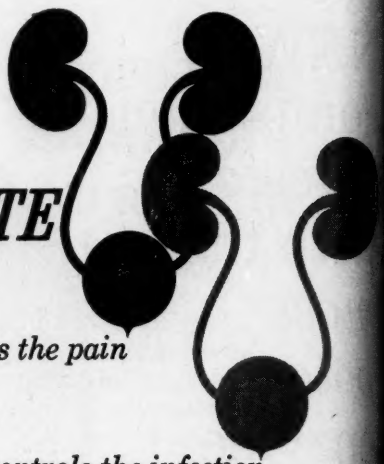
Organon

A product of origin[illegible] Organon research, lipancreatin provides *for the first time in digestant preparations a known, constant amount of fat-digesting lipase* in addition to trypsin and amylase. It surpasses in assayable digestive activity all presently available pancreatin preparations.

In urinary tract infection

NEW "THIOSULFIL"-A FORTE

Brand of sulfamethizole with phenylazo-diamino-pyridine HCl



alleviates the pain

controls the infection

"THIOSULFIL"-A FORTE combines the *sulfonamide specific* for urinary tract infection with a *potent analgesic* for prompt, soothing relief of local discomfort.

Recommended in *acute* urinary tract infection, such as cystitis, urethritis, pyelitis, pyelonephritis, and prostatitis due to bacterial infection amenable to sulfonamide therapy. "Thiosulfil" has been effective against the following urinary pathogens: *Proteus vulgaris, Pseudomonas aeruginosa, Escherichia coli, Streptococcus fecalis, Escherichia intermedium,* and *Aerobacter aerogenes.* In individual cases, sensitivity of the organisms may vary. Sensitivity tests, preferably by the tube dilution method, should be done first, for guidance as to alternate therapy in case "Thiosulfil"-A Forte does not control the infection.

USUAL DOSAGE: Adults: 2 tablets, four times daily.
Children: (9 to 12 years): 1 tablet, four times daily.

WARNING: Due to the high solubility in body fluids of "Thiosulfil" and its acetyl form, the hazards of renal tubule obstruction are minimized. The usual precautions exercised with sulfa drugs generally should, however, be observed. In those rare instances where exanthemata, urticaria, nausea, emesis, fever or hematuria, are encountered, administration should be discontinued.

CONTRAINDICATIONS: (1) a history of sulfonamide sensitivity and (2) due to the phenylazo-diamino-pyridine HCl component, renal and hepatic failure, glomerulonephritis, and pyelonephritis of pregnancy with gastrointestinal disturbances.

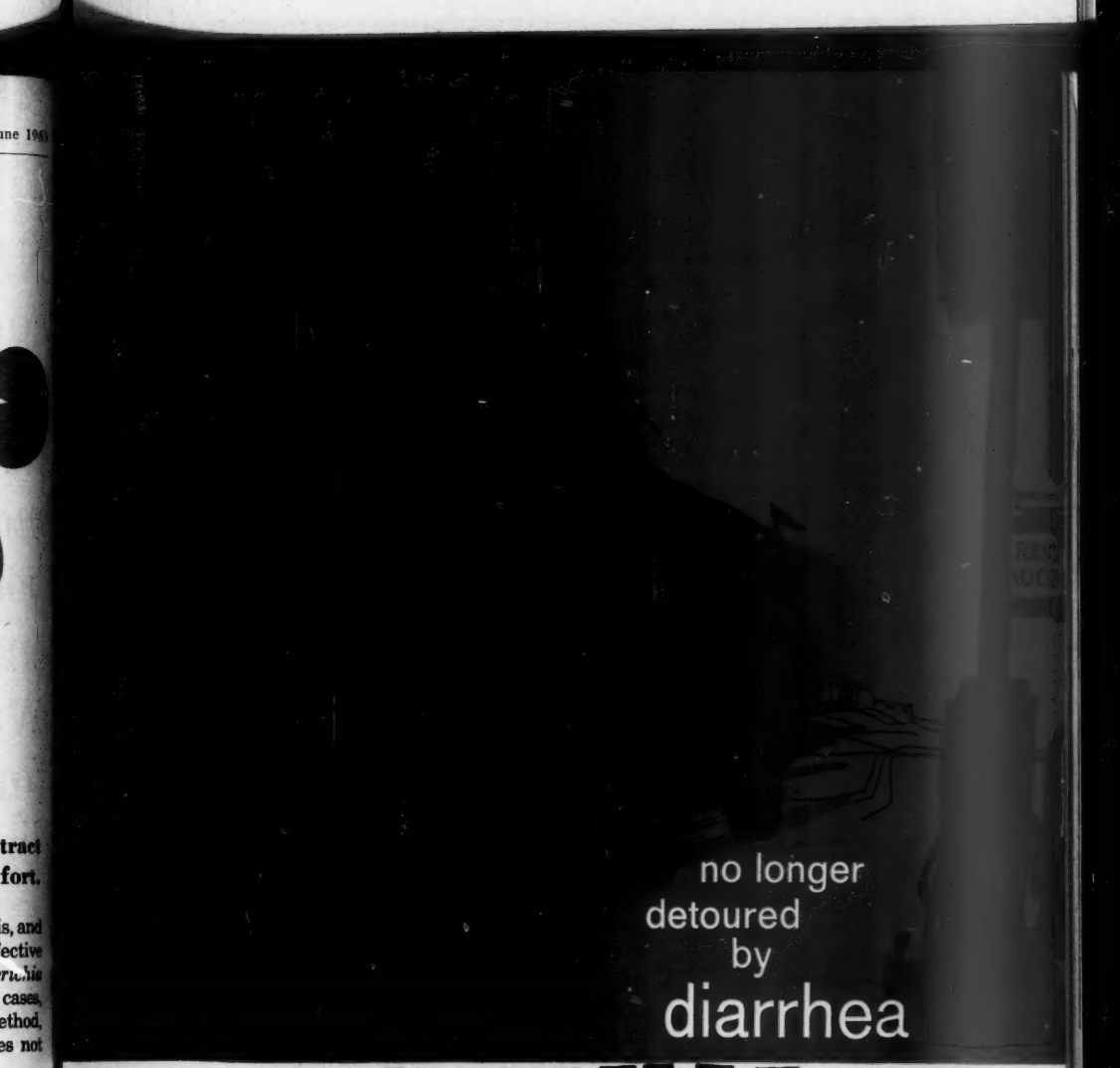
SUPPLIED: "Thiosulfil"-A Forte—No. 783: Each tablet contains sulfamethizole 0.5 Gm., and phenylazo-diamino-pyridine HCl 50.0 mg., in bottles of 100 and 1,000.

also available: "Thiosulfil"-A—No 784: Each tablet contains sulfamethizole 0.25 Gm., and phenylazo-diamino-pyridine HCl 50.0 mg., in bottles of 100 and 1,000.

USUAL DOSAGE: *Adults:* 2 tablets, four times daily. *Children:* (9 to 12 years): 1 tablet, four times daily.

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6122



DONNAGEL®

Donnatal® with Kaolin and Pectin compound

Robins

DONNAGEL's comprehensive antidiarrheal formulation gives the green light to normal activity, through its fast and dependable control of intestinal hypermotility.

Each 30 cc. (1 fl. oz.) of DONNAGEL contains:

Kaolin	6.0 Gm.	Natural belladonna alkaloids:	
Pectin	142.8 mg.	hyoscyamine sulfate	0.1037 mg.
Phenobarbital (1/4 gr.)	16.2 mg.	atropine sulfate	0.0194 mg.
		hyoscine hydrobromide	0.0065 mg.

also available

DONNAGEL WITH NEOMYCIN · DONNAGEL-PG

DONNAGEL plus neomycin sulfate 300 mg. (as neomycin base) 10 mg./5 cc. (1 tsp.) or 30 cc.

DONNAGEL plus powdered opium USP 24.0 mg. per fl. oz. (equivalent to paregoric 6 ml.) This is the usual adult dose.

All three forms available in bottles of 6 fl. oz.

controls the acutely agitated patient

SPARINE is a versatile agent for the control of acute manifestations of severe mental and emotional disturbances.

Indicated for the prompt management of your patients displaying:

- central nervous system excitation, apprehension, or acute agitation
- postalcoholic syndrome, including delirium tremens and acute hallucinosis
- symptoms of drug withdrawal
- anxiety, pain, nausea, vomiting, hiccups during medical emergencies

With SPARINE in your bag, you are always prepared to cope with emergencies such as acute alcoholism and severe emotional disturbances. Useful in maintaining control.



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HYDROCHLORIDE

Promazine Hydrochloride, Wyeth

SPARINE effectively controls central nervous system excitation, allays apprehension and anxiety, calms the agitated patient and is a useful adjunct to the management of mental and emotional disturbances. It is effective in the management of alcohol-induced syndromes (delirium tremens, acute hallucinosis, acute tremulousness, inebriation) as well as the withdrawal symptoms of drug addiction. Both acute and chronic psychiatric illnesses respond to SPARINE therapy. SPARINE has been found to be useful in the management of nausea and vomiting of either central nervous system or gastric reflex origin. SPARINE effectively facilitates the action of analgesics and central nervous system depressants. It has been used as an adjunct to surgical sedation, allaying apprehension and reducing the dosage requirements for narcotics, analgesics and sedatives. SPARINE may be used as an aid in diagnostic and therapeutic regimens. Such nonspecific symptoms as anxiety, pain, vomiting, nausea and hiccups frequently make more difficult both diagnosis and therapy of organic disease. SPARINE allays such symptoms without masking physical, neurological or laboratory findings.

Directions: For maximal therapeutic benefit the amount, route of administration and frequency of dose should be governed by the severity of the condition treated and the response of the patient. Oral administration should be used whenever possible; parenteral administration should be reserved for uncooperative patients or when nausea and vomiting interfere with oral administration. SPARINE *when used intravenously should not exceed a concentration of 25 mg. per cc.; injection should be given slowly.* Dilute 50 mg. per cc. concentration with equivalent volume of physiological saline before I.V. use. Avoid injection around or into the wall of the vein. Inject only into vessels previously undamaged by multiple injections or trauma.

In the management of acutely agitated patients, SPARINE should be given I.V. in initial doses of 50 to 150 mg. If the desired calming effect is not apparent within 5 to 10 minutes, additional doses up to a total of 300 mg. may be given. (*In the acutely inebriated patient, the initial dose should not exceed 50 mg.*) Once the desired effect is obtained, SPARINE may then be given I.M. or orally in maintenance doses of 10 to 200 mg. at four to six hour intervals. *In less severe disturbances,* initial oral therapy may be satisfactory. When tablet medication is unsuitable or refused, SPARINE Syrup may be used.

As an antiemetic, usual dose is 25 to 50 mg. repeated at four to six hour intervals. When oral route is not feasible, 50 mg. I.V. or I.M. will usually control the symptom, but oral medication should be initiated as soon as feasible. *In medical emergencies,* to allay apprehension and facilitate diagnosis or therapy, SPARINE should be given I.V., I.M. or orally in 50 to 200 mg. doses. See direction circular for details. *In the management of pain associated with malignancy or chronic disease,* SPARINE may be administered orally or I.M. in 25 to 50 mg. doses repeated at four to six hour intervals to allow for reduced dosage of analgesics.

Precautions: Although rare, drowsiness, dizziness and transitory postural hypotension may occur. If a vasopressor drug is indicated, norepinephrine is recommended, since SPARINE reverses the effect of epinephrine. Agranulocytosis has been reported in only 18 cases in about 3½ million patients. If, however, signs of cellular depression —sore throat, fever, malaise—become evident, discontinue SPARINE, check white blood cell count, and initiate antibiotic and other suitable therapy if indicated. Seizures, reported as occurring during SPARINE therapy, occur usually with rapid large increases in dose and at a daily dosage above 1 Gm. Caution must be exercised when administering SPARINE to patients with a history of epilepsy. There are reports in the literature indicating that patients may develop jaundice and/or liver dysfunction when taking promazine if they have previously taken chlorpromazine even though they did not show jaundice during chlorpromazine therapy. Avoid perivascular extravasation or intra-arterial injection, as severe chemical irritation or inflammatory response may result.

Because of its enhancing action on analgesics and central nervous system depressants, give them only in reduced dosage with SPARINE. Do not use in comatose states due to central nervous system depressants (alcohol, barbiturates, opiates, etc.). Use with caution in patients with cerebral arteriosclerosis, coronary heart disease, or other conditions where a drop in blood pressure may be undesirable.

For further information on prescribing and administering SPARINE, *see descriptive literature, available on request.*

Wyeth Laboratories Philadelphia 1, Pa.

in the wide middle region of pain



Percodan®

Salts of Dihydrohydroxycodeinone and Homatropine, plus APC

TABLETS

fills the gap between mild oral and potent parenteral analgesics[1,2]

- **acts in 5-15 minutes**
- **relief usually lasts 6 hours or longer**
- **toleration excellent... constipation rare**
- **sleep uninterrupted by pain**

Each Percodan® Tablet contains 4.50 mg. dihydrohydroxycodeinone HCl, 0.38 mg. dihydrohydroxycodeinone terephthalate (warning: may be habit-forming), 0.38 mg. homatropine terephthalate, 224 mg. acetylsalicylic acid, 160 mg. acetophenetidin, and 32 mg. caffeine.

AVERAGE ADULT DOSE
1 tablet every 6 hours
May be habit-forming
Federal law permits oral prescription

Also Available
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1. Blank, P., and Boas, H.: Improved analgesia for moderate pain, Ann. West. Med. & Surg. 6:376, 1952. 2. Bonica, J. J., et al.: The management of postoperative pain with dihydrohydroxycodeinone (Percodan): Evaluation with codeine and placebo, West. J. Surg. 65:84, 1957. 3. Cass, L. J., and Frederick, W. S.: A controlled study in pain relief, M. Times 84:1318, 1956. 4. Chasko, W. J.: Pain-free dental surgery. Postoperative extension of the pain-free state, J. District of Columbia Dent. Soc. 31:3, No. 5, 1956. 5. Cozen, L.: Office Orthopedics, ed. 2, Philadelphia, Lea & Febiger, 1953, pp. 138, 145, 156, 234. 6. Nicolson, W. P., and Skandalakis, J. E.: Control of postoperative pain, J.M.A. Georgia 46:471, 1957. 7. Pinel, C. E., and Nicklin, F. W.: Percodan for pain in industrial practice, Industr. Med. 23:510, 1954; abstracted, Clin. Med. 3:1008, 1956; Current M. Digest 22:135, No. 3, 1955.

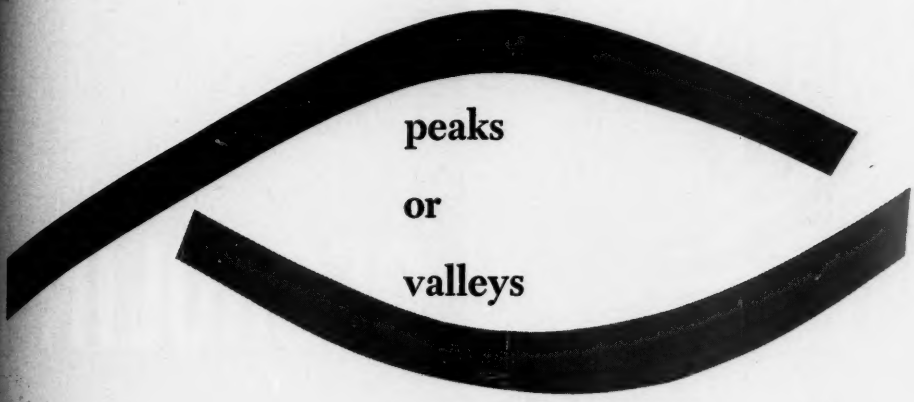
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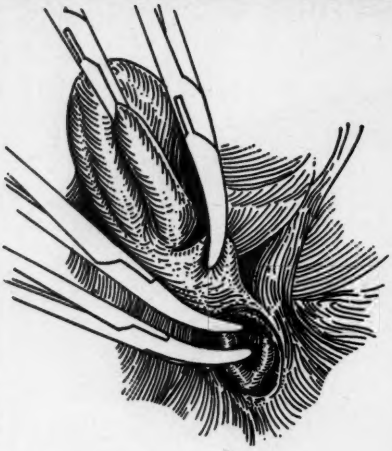
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Source: **Farris, J. M., and Smith, G. K.: M. Clin. North America *43*:1133 (July) 1959.**

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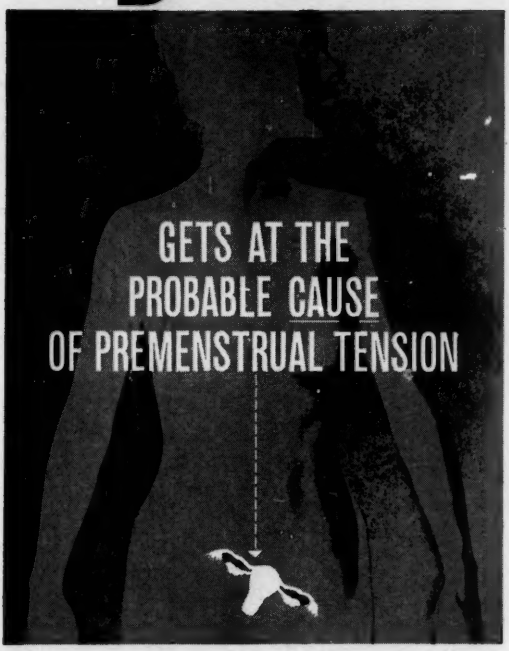
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J.A.M.A. **170**:1647 (Aug. 1) 1959 J.A.M.A. **172**:154 (Jan. 9) 1960
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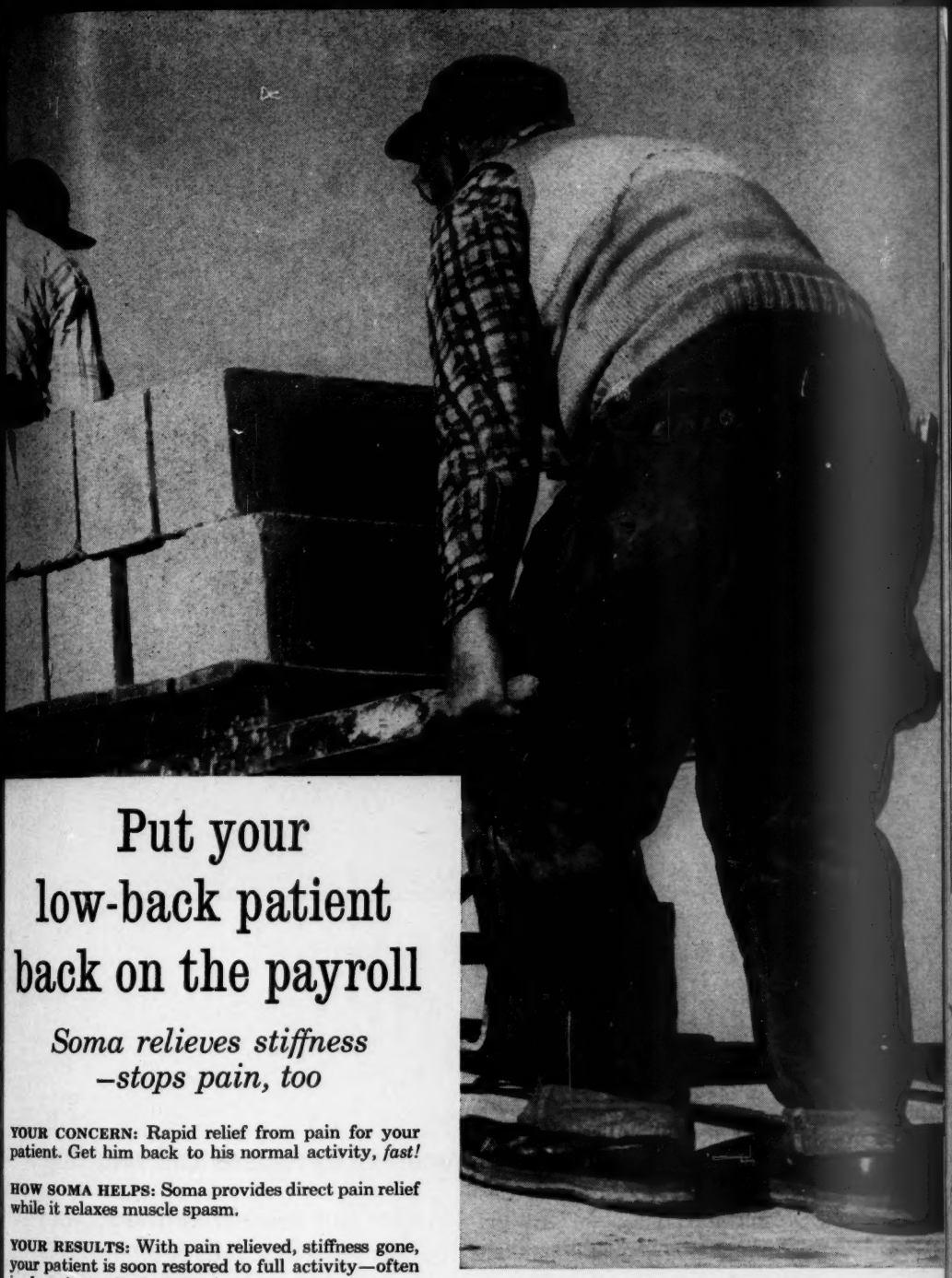
*Edelstein, A. J.: Pennsylvania M.J. 62:1831 (Dec.) 1959.

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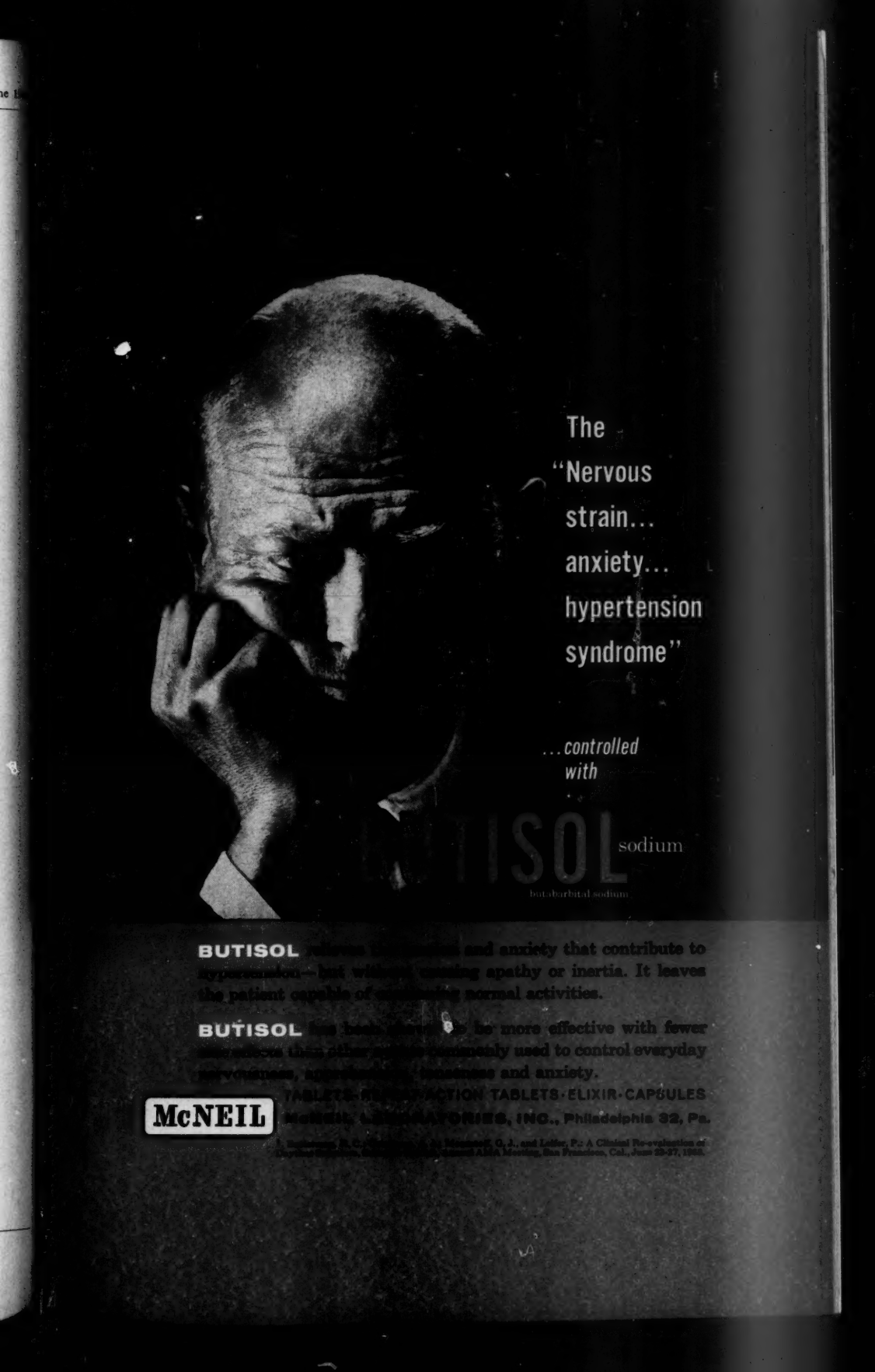
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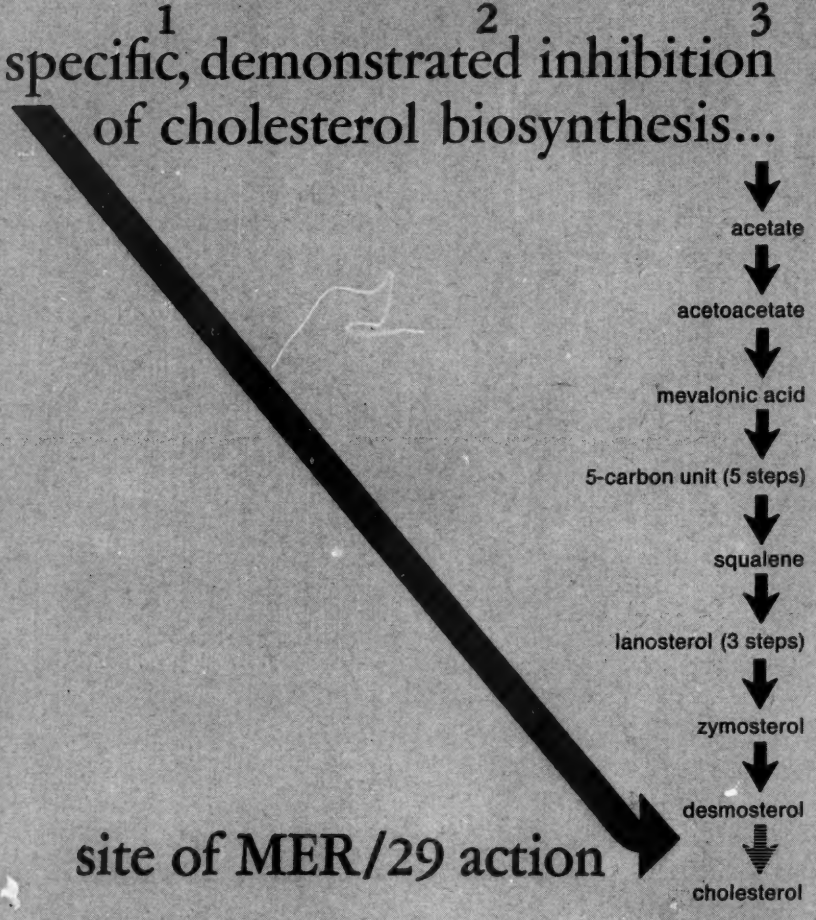
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Course No. 3, THE INTERNIST'S ROLE IN THE PRE AND POSTOPERATIVE CARE OF THE SURGICAL PATIENT, Mayo Clinic, Rochester, Minn.; Hugh R. Butt, M.D., F.A.C.P., and James C. Cain, M.D., F.A.C.P., Co-Directors.								X															
Course No. 4, ADVANCES IN ELECTROCARDIOGRAPHY, New York University Medical Center, New York, N. Y.; Charles E. Kossmann, M.D., F.A.C.P., Director.												X											
Course No. 5, INTERNAL MEDICINE—TODAY'S PROBLEMS IN DIAGNOSIS AND MANAGEMENT, AND TOMORROW'S PROJECTIONS, Ochsner Foundation Hospital, New Orleans, La.; A. Seldon Mann, M.D., F.A.C.P., and William D. Davis, Jr., M.D., F.A.C.P., Co-Directors.																		15–18					
Course No. 6, MEDICAL GENETICS, The University of Michigan Medical School, Ann Arbor, Mich.; James V. Neel, M.D., F.A.C.P., Director.																				29–1			
Course No. 7, PATHOLOGIC PHYSIOLOGY OF THE BLOOD DYSCRASIAS, Washington University School of Medicine, St. Louis, Mo.; Carl V. Moore, M.D., F.A.C.P., William J. Harrington, M.D., F.A.C.P., and Edward H. Reinhard, M.D., F.A.C.P., Co-Directors.																						X	
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—National Heart Institute: Diet, Hormones, and Atherosclerosis..., Bethesda, Md., U.S. National Institutes of Health, 1958.

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(1) Brooks, L. H.: Dis. of Colon & Rectum, v. 1, no. 5, 1958

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1. Bovet, D., and Nitti-Bovet, F.: Arch. Internat. de pharmacodyn. et therap. 83:367, 1946. 2. Melville, K.I., and Lu, F.C.: Canad. M.A.J. 65:11, 1951. 3. Fuller, H.L. and Kassel, L.E.: Antibiotic Med. & Clin. Therapy 3:322, 1956. 4. Elsfelder, H.W. et al.: J. Am. Geriatrics Soc. 8:62, 1960.

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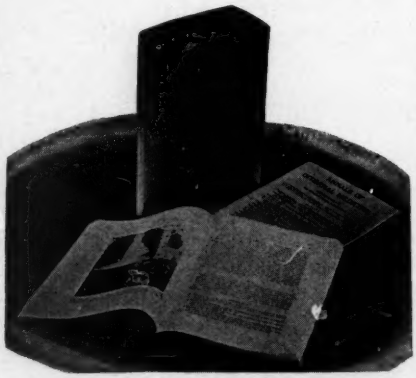
1. Ostfeld, A. M.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959. 2. David, N. A.; Logan, N. D., and Porter, G. A.: Evaluation of Thioridazine (Mellaril), a New Phenothiazine, in The Hospitalized Patient, A.M. & C.T. 7:364 (June) 1960.

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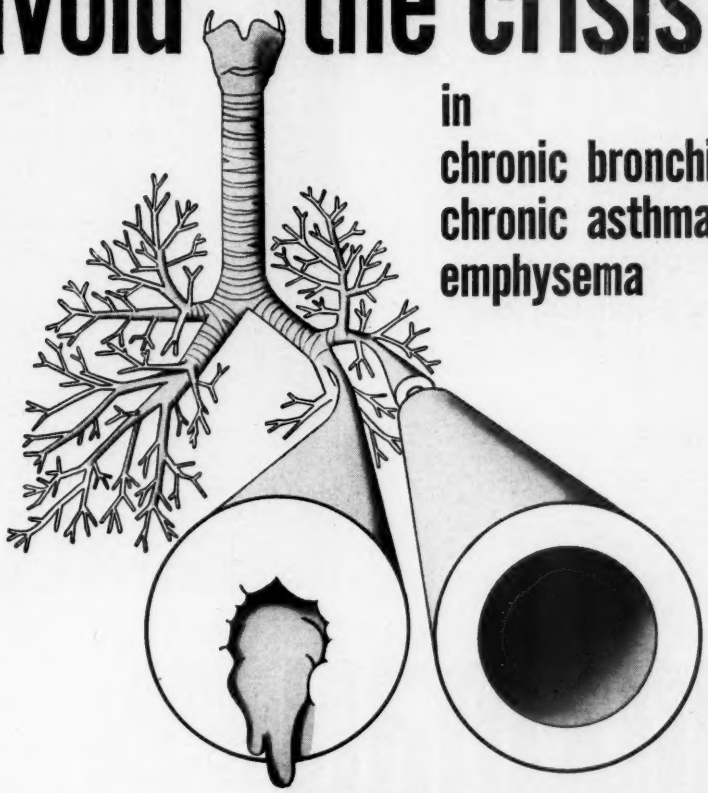
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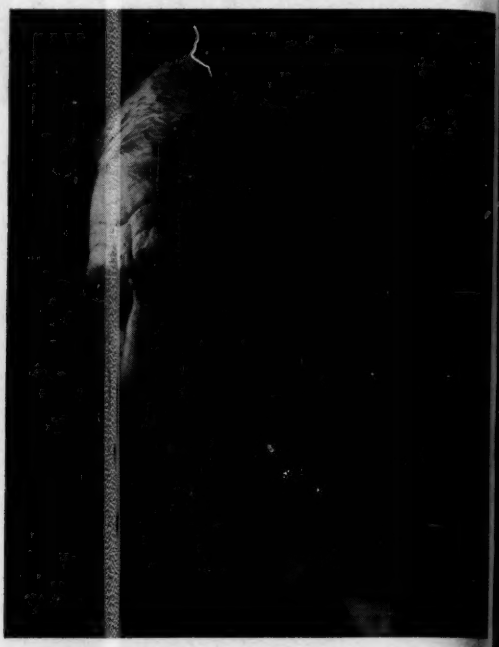
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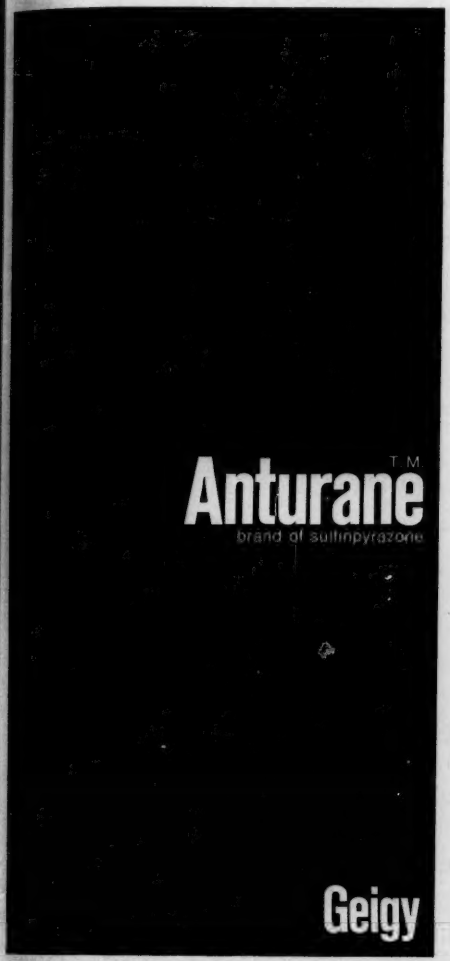
Doxidan effects easy defecation, free of pain, strain and cramping.[1] As a result, "rebound constipation" is largely obviated and the tendency toward laxative dependency is greatly reduced.

FORMULA: Each capsule contains 50 mg. danthron (1, 8-dihydroxyanthraquinone) and 60 mg. calcium bis-(dioctyl sulfosuccinate).

DOSAGE: Adults and children over 12, one or two capsules. Children, age 6 to 12, one capsule. Administered at bedtime for 2 or 3 days or until bowel movements are normal. Supplied in bottles of 30 and 100 soft gelatin capsules.

1. Beil, A. R. and Brevetti, R. E.: Management of constipation during the puerperium, New York State J. Med. 60:2706-2707, September 1, 1960.
2. McCarthy, E. V.: Calcium bis-(dioctyl sulfosuccinate) in treatment of constipation, Clin. Med. 7:2257-2259, November, 1960.

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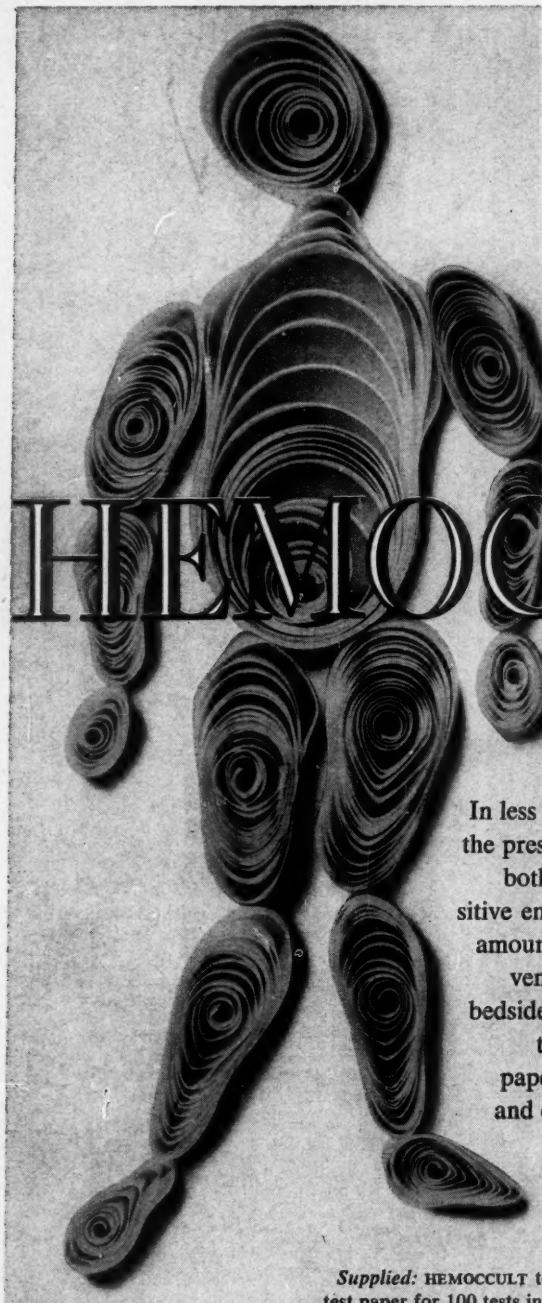
References: 1. Seegmiller, J. E., and Grayzel, A. I.: J.A.M.A. 173:1076, 1960. 2. Yü, T. F., Burns, J. J., and Gutman, A. B.: Arth. & Rheumat. 1:532, 1958. 3. Kersley, G. D., Cook, E. R., and Tovey, D. C. J.: Ann. Rheumat. Dis. 17:328, 1958. 4. Gutman, A. B., and Yü, T. F.: Bull. New York Acad. Med. 34:287, 1958.

Full product information regarding dosage, side effects, precautions and contraindications available on request.

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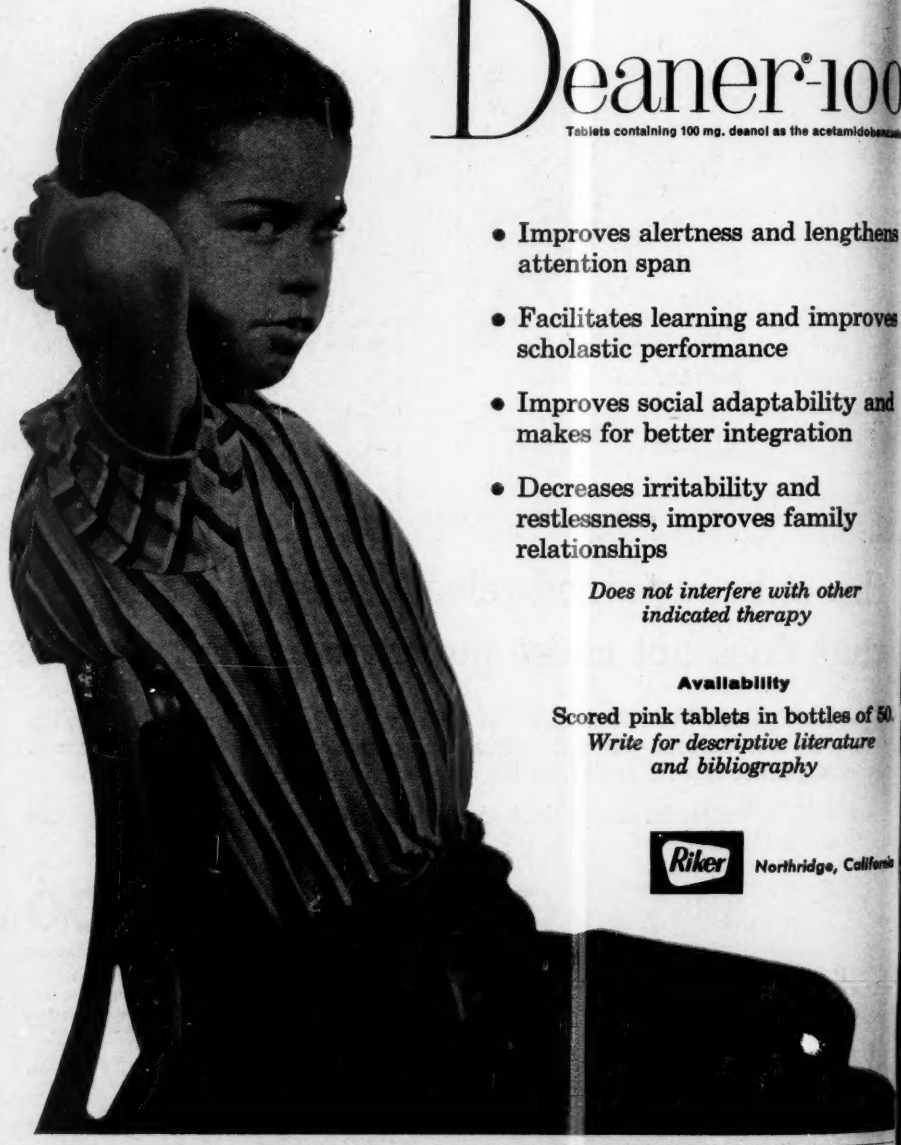
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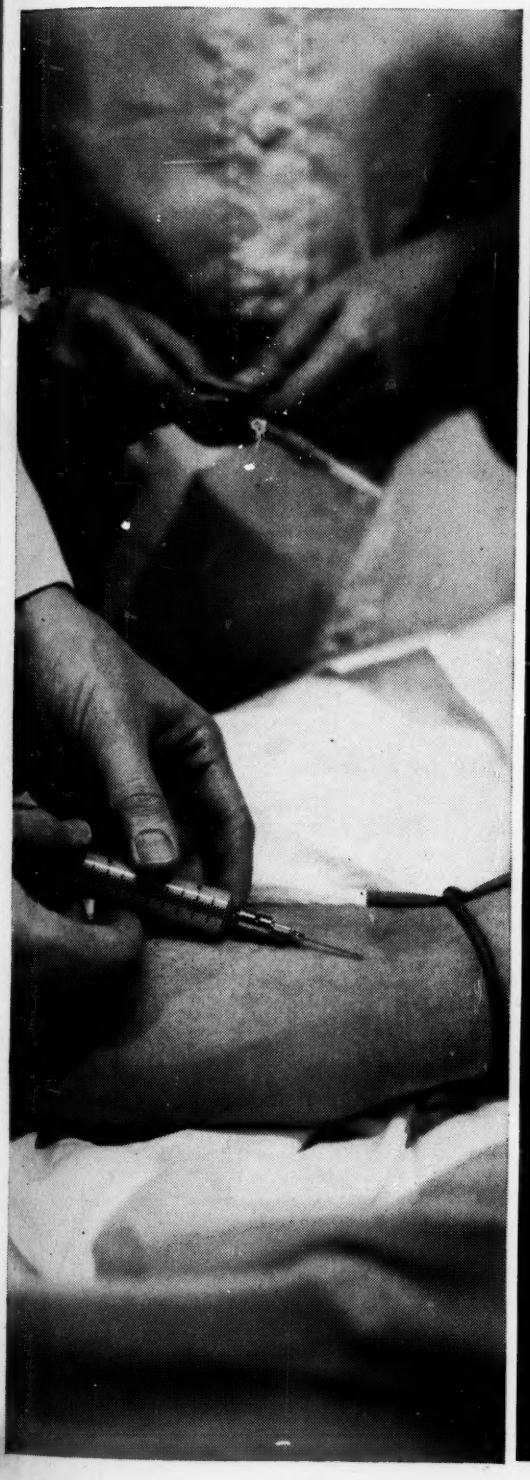
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